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CONSIDERATIONS BEARING ON THE TREATMENT OF ARTHRITICS.*

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DEVELOPMENTS have taken place in our concept of the arthritic problem. The field is not dominated, as was so long the case, by the limited hypothesis that arthritis is due to focal infection alone. For many years this was regarded as the only factor to which attention need be given.

It was early apparent to a small number, however, because of the interest which these workers felt in certain physiologic aspects of the disease, that these other aspects or factors also exert determining influences. Now the profession can hear with equanimity, from an interesting recent study of 200 cases of rheumatoid arthritis, that chronic focal infection plays a "comparatively unimportant rôle."

However justified in fact such iconoclasticism toward focal infection may eventually prove to be, other phases of physiology are independently coming in for more attention. As long ago as 1920 the writer stated that any observer can satisfy himself that such an episode as pneumonia or pregnancy may result, at least temporarily, in escape from symptoms of arthritic disease. Other experiences led him to believe and teach that there are functional changes underlying arthritic disability which pave the way for organic change and are indeed not wholly irreversible.

This principle of reversibility is more or less accepted for fleeting rheumatic disability, such as is encountered in a stiff neck from which one recovers after a little aspirin but is largely ignored or overlooked in more advanced stages where it is, however, none the less operative.

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The arthritic is abnormal not only because of deviations within his joints but also because of deviations within his body elsewhere, more or less open to modification. Hench has recently well developed the hitherto buried observation that icterus may also initiate a dramatic escape from the symptoms of the disease.

It is refreshing to hear from him that "the pathologic physiology of rheumatoid arthritis is more rapidly reversible than previously supposed." Rawls[6] has recently adduced evidence to the same end and many illustrations of the truth of this principle are to be observed.

Thus, for one example, on nearly every hand systemic rest is acknowledged to be the most useful single basic factor in treatment of both great types. But rest is not a simple entity; it is a mosaic of countless components, some of which may do harm as well as good, all of which are susceptible of more refined application than they are usually accorded. There is perhaps no fixed entity such as rest, *per se*, since rest is a relative term.

However, the processes comprised by rest can be analyzed and largely separated so as to permit of appropriate application. Rest to the nervous system, for example, is not a complete negation of activity. It is a specific prescription for a different kind of physiologic performance, which can even be abetted pharmacologically. Rest to the vascular system may be regarded equally specifically as an adjustment of physiologic requirements to the capacity of the system, especially the capillary beds.

The gastro-intestinal system may be made equally to perform, by rest, in a more effective manner and the processes of nutrition can be similarly bettered.

Undoubtedly a better concept would be obtained of that whereof rest consists, if, instead of a blanket prescription for rest, with all that is hidden and unobserved beneath it, the physician should explicitly order, severally and separately, the specific things which rest brings about. Probably few physicians could do this without study, and yet it illustrates only one of the therapeutic approaches to the arthritic problem.

Use of "rest" in this broad way, however, is not to be interpreted as a generic panacea for arthritics. It is brought forward rather as a comprehensive, though fragmentary, method of approaching that betterment of function, in many systems of the body, which makes toward a so-called reversal of the arthritic process. Such betterment of function is not necessarily optimal or complete when induced in this way alone and it is certain that treatment of arthritics cannot be reduced to a catchword, even one so important as "rest."

The chief point at issue is that without awaiting influences yet unmapped, we have already available many, sometimes all, of the varied mechanisms necessary to a true reversal of the deranged physiologic processes leading to arthritis.

In his presidential address to the American Society for Clinical

Investigation, Paul recently stated with commendable courage, "A dominant thing about some of our present notions of causative factors is that unless they fit into a modern pattern of our own liking, they are apt to be overlooked. Of late years conservative opinion does not allow anything to be really considered 'etiology' unless we can succeed in getting it into a test tube." Perhaps nowhere have these remarks more relevance than in the multi-facetted problem of arthritis.

With a general growth of interest in the physiologic deviations of the syndrome it becomes important to reaffirm that certain clinical and physiologic considerations should receive more attention.

An important lesson has been taught by study of the mild deficiency syndromes. The reciprocal factors making toward, or away from, these states do not necessarily operate separately to produce or cure the disease. Expenditure of energy, imbalance of foodstuffs, infection or minor changes in gastro-intestinal function, may be as instrumental, in the production of a deficiency syndrome, as is a true primary inadequacy.

Clinical experience usually runs ahead of precise evaluation of its components and to negative comparable influences in the field of arthritis because they do not constitute the sole cause, is to fail to see the problem whole in terms of practical therapy.

The writer believes that even in attempting to evaluate the influence of focal infection, as in the interesting article referred to earlier, the conditioning factors which make infection operative or otherwise must be equally evaluated, if the conclusions are to have any significance. To state that in a given series, removal of infection is unsuccessful may be simply to state that removal is unsuccessful under conditions such that it could hardly be expected to be otherwise. Great injustice may thus be done to the significance of removing infection if it be viewed apart from its real setting; surgically rather than biologically, so to speak. Incidentally, removal of infection is often not so complete as supposed.

Undue difficulty is apparently encountered on the part of some who treat arthritics. Perhaps one reason is not far to seek. Much recent dogma has been too strong, both pro and con. Perhaps the negative postulate is now a greater offender than the enthusiastic claims of yesterday.

The fact that faulty posture in respect to lordosis, a narrow costal angle and visceroptosis is not "the cause" of arthritis and that betterment of these handicaps does not alone "cure" all cases, does not justify zealous sceptics in discounting useful fragments of a philosophy possibly wider than their own.

Again, the fact that Raynaud's disease is not accompanied by classical arthritis does not constitute evidence that disturbances in the finer circulation bear no relation to arthritis. All clinical experience negatives such an oblique outlook.

In few syndromes is nutritional imbalance more observable than

in the arthritic. Atrophy of bone, subvitaminosis, faulty hematopoiesis, altered plasma proteins and tissue edema are common spectacles.

Some of these deviations are open to prompt amelioration; but, in general, little refinement of approach is evident in attempting to prevent or correct them.

Again, the functions of the gastro-intestinal tract present a chapter of physiology too complicated to be dismissed cavalierly. To mention only a few considerations, Ghormley *et al.*[5] have observed recently an increased incidence of osteoporosis in elderly persons. They point out that protracted deficiencies in basic nutrition from poor dietary habits may impair the health of the adult and contribute to disabilities commonly attributed to old age. Apart from the intake of calcium, vitamin D and imbalance of the main caloric foods in the diet, the ability to absorb mineral salts from the intestinal tract grows less with age. Ivy has shown the importance of gastric function in mineral metabolism, even in puppies. The recognized decrease in gastric HCl of older persons may have consequences more significant than is generally realized. Edström[4] recently reported a depressive secretory anomaly of the stomach in 30% of atrophic arthritics. In a review of 100 normals and 100 arthritics of both types from the Roentgen ray standpoint, Spackman has observed clear-cut anatomic and physiologic deviations in the lower gastro-intestinal tract of the arthritic groups. The writer believes that neither great type of arthritis lies wholly without the framework of these general concepts.

By the same token, dogmatic allocation of hypertrophic arthritis to age and trauma alone leaves unbridged a philosophic chasm into which many arthritics are falling. Among other evidences indicating systemic disturbance, Dandurand and Scull have recently observed reducing bodies other than glucose in the blood of hypertrophic cases in amounts significantly higher than in normal subjects.

The point of view from which the observer regards the arthritic scene has too much importance. To him who learns arthritis through bacteriology, few other phases of medicine may seem to touch it. To the pathologist, the microscope alone reveals what is worthy of notice. To the practitioner, basic considerations may seem futile since his patients await relief from pain and want it now. Like too many bands in a parade, only cacophony may result, unless each be coördinate with the others. The parade need not be so much out of step, however, as it seems to be.

Between a strong therapeutic nihilism on the one hand and wishful thinking on the other, there is a middle ground in the care of arthritics, within which many experienced students and clinicians find cause for great optimism. Successful therapy within this ground cannot be achieved by means of any alleged panacea, or, by means of such platitudes as "good hygiene, fresh air and keeping the bowels open." It can be frequently achieved, however, on the basis of a

systematic and directional attempt at readjustment of all the dislocated physiologic processes accompanying and largely characterizing the disease. This usually requires sustained study of arthritis from this angle. The lesson is not quickly learned and cannot be compressed into the narrow limits of an address. A mere titular recital of the steps involved no more equips the student than it does in major surgery

For any one treating arthritics to lack a good working familiarity with the disease so viewed, as well as with the work of serious students in general, is to reveal a situation which this Society can properly deplore and the laity properly criticize. There is small doubt, however, that in some quarters such a situation exists today.

It is possible that the future may reveal some single factor causative of the disease. Thus Collier[3] has recently observed a transmissible arthritic disease of rats, and Sabin[7] has reported a "pleuropneumonia-like" organism comparably influential in mice.

By the same token, the future may hold some single remedial agency which will reach to or near the heart of the oak but we are not yet in possession of it. Perhaps gold will prove as valuable to the patient in his body as it has proven to be in his pockets. The somatic substrate of the arthritic subject, however, may not be so easily altered and usually needs a different approach. Biologic experience teaches increasingly that the cause of disease processes usually lies back of the firing line, so to speak. Binger well expresses this point of view: "Our attitude toward disease is changing. It is no longer satisfactorily explained as a catastrophic invasion by noxious agents, a belief handed down to us not by bacteriologists alone. . . . We know now that it requires more than the tubercle bacillus to make a man tuberculous, more than a specific antigen to produce an asthmatic attack and more than pneumococci to precipitate an attack of pneumonia. . . . There is now a growing body of evidence which leads to the belief that . . . disease, be it infectious, allergic, functional, organic or degenerative, has its developmental history in which the whole personality is involved."

Whether we like it or not, we must today face the fact that, lacking that final illumination of arthritis which is our goal, we are definitely expected in the present half light to use all such well considered measures as are available to us, or else deserve the reproaches of society. At last analysis the care of arthritics as a whole falls upon the general practitioner. He properly takes his therapeutic cue from those studying the disease and unless a reasonably wide-angled and, above all, a coördinated program be presented to him he cannot be blamed if he turns from academic negativism to the samples sent him by a drug house. To know how to utilize the components of rest; to stimulate here and sedate there; to appreciate the significance of deficiencies or surfeits, to recognize and correct them; to discover an infectious or other morbid nidus, to understand whether and when to remove it; to reëducate the patient toward his

problem; to adjust his somatic and local mechanics; in sum, to "equilibrate" the arthritic and treat him as few sufferers from other diseases are treated—this constitutes, in the opinion of the writer, at least an approach towards a specific therapy which must be experienced to be understood.

There is at the moment a real danger that in our separate quests for the cause of arthritis we are losing some perspective in the cause of arthritics. The chief purpose of this paper is, therefore, to present two objectives:

First. Avoidance of the exclusive outlook in this vexed field and the maintenance of a balanced perspective toward *all* deviations presented by the arthritic;

Second. Recognition that effective therapy often depends upon coördinating the influences of many physiologic processes, and that utilization of these influences can be achieved only by those who recognize the importance of this coördination and are sufficiently desirous of bringing it about.

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THE USE OF SULFAPYRIDINE* IN THE TREATMENT OF GONOCOCCAL URETHRITIS IN THE MALE

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The use of sulfapyridine (2(para-amino-benzene-sulfonamido) pyridine) was first reported by Whitby[10] in May, 1938, in the treatment of experimental infections in animals. Following shortly upon the reports of the drug's phenomenal clinical success in the treatment of pneumococcal pneumonia, Lloyd, Erskine and Johnson[7] in England,

* Merck & Co., of Rahway, N. J., kindly supplied the sulfapyridine used in this study.

Durel[3] in France, and later Bowie[1] reported preliminary results which suggested that sulfapyridine would prove to be at least as successful as sulfanilamide in the treatment of gonorrhea.

These results led us to a trial of the treatment of gonococcal urethritis in the male with sulfapyridine. We were early[5,5b] impressed with its efficiency and felt justified in continuing our study with a larger number of patients.

Material. Our material consisted of 80 male patients with gonococcal urethritis observed in the Urological Out-Patient Department of the Hospital of the University of Pennsylvania. Of these, 29 were white and 51 negro ranging from 17 to 48 years. Following Pelouze[5a] and Eisendrath and Rolnick,[4] we have classified as acute those cases of less than 3 months' duration, as subacute those lasting between 3 and 6 months and as chronic those over 6 months' duration. There were 70 cases of acute urethritis of which 31 were anterior only and 39 antero-posterior; 6 cases of sub-acute urethritis of which 3 were anterior and 3 were antero-posterior, and 4 cases of chronic urethritis, all of which were antero-posterior urethral infections. Forty-one of the patients had had previous attacks of gonorrhea, from 1 to 7 times. When presenting themselves for treatment, 1 had inguinal adenitis, 3 had bilateral epididymitis, 1 unilateral epididymitis and 1 gonorrheal arthritis. Fifteen patients had had one or more of the following drugs in the treatment of his present infection without success: sulfanilamide, sulfanilyl-sulfanilamide, neo-protonsil and para-amino-benzene-sulphonamido-d-camphor sulfonate; 7 had had a combination of local therapy and one or more of the above mentioned drugs and 6 had had only local treatment.

Procedure. Gram negative intracellular diplococci were demonstrated by means of Gram stain of the urethral discharge in all of the patients before treatment was instituted. The patients were seen, when possible, at 2- to 3-day intervals, the urine being examined by the two-glass test. Gram stains of the urethral discharge were made frequently. A complete blood count was obtained on the day treatment was begun and was repeated in 5 to 7 days, and oftener if thought necessary. In the majority of cases blood sulfapyridine levels were taken after 4 days and again after 10 and 14 days.

Dosage. The dosage scale employed was chosen arbitrarily and adhered to routinely unless some untoward reaction occurred. This consisted of 3 gm. of sulfapyridine a day for 4 days and then 2 gm. a day for 6 to 10 days given in divided doses. Sulfapyridine was not administered continuously over more than a 2 weeks' period of time except in 1 hospitalized patient.

Criteria of Cure. The following provocative tests of cure were employed when the urine had remained clear for from 4 to 6 days following discontinuance of clinical symptoms:

1. Massage of the prostate and seminal vesicles;
2. Passage of bougies and sounds with digital stripping of the anterior portion of the urethra;
3. Consumption of alcoholic drinks;
4. Sexual intercourse with a condom;
5. One to two negative cultures* of the prostatic secretion.

* Sediment from centrifuged first portion of voided urine after prostatic massage grown on "chocolate" ascitic agar in 10% CO_2. Identification of colonies made by oxidase reaction and sugar fermentation.

Results. Of the 80 patients treated with sulfapyridine, 17 either failed to complete the course of treatment or failed to complete the tests of cure. This left 63 patients, the majority of whom were followed 2 or more months. Of the patients followed, 54 had acute urethritis, 42 (77.8%) being cured; 4 had sub-acute urethritis, all of whom were cured, and 4 had chronic urethritis, all but 1 being cured. There were followed 26 patients with anterior urethritis, 21 (80.8%) being cured, and 37 with antero-posterior urethritis of whom 29 (78.4%) were cured. In all, there were 50 patients (79.2%) who were classified as cures (Table 1).

TABLE 1.—RESULTS OF TREATMENT WITH SULFAPYRIDINE.

	No. of patients.	Cures.		No. of defaulters.	No. of failures.	Average duration of discharge of cures, days.
		No.	%.			
Total series	80	50	79.2	17 (21%)	13	2.77
Acute urethritis	70	42	77.8	16	12	2.93
Anterior	31	18	78.3	8	5	3.42
Posterior	39	24	77.4	8	7	2.5
Subacute urethritis	6	5	100.0	1	0	1.8
Anterior	3	3	100.0	..	..	2.3
Posterior	3	2	100.0	..	..	1.0
Chronic urethritis	4	3	75.0	..	1	2.3
Posterior	4	3	75.0			
Anterior urethritis	34	21	80.8	8	5	3.3
Posterior urethritis	46	29	78.4	9	8	2.4

The average duration of urethral discharge in the cured patients after onset of therapy was 2.77 days. This, of course, represents a remarkable advance over the older forms of treatment with sedation and local therapy, with which, in the experience of this Department, 10 days to 2 weeks almost invariably elapsed before the same improvement occurred. In the cases of acute urethritis, the average duration of discharge was 2.93 days; in the subacute cases, 1.8 days; the chronic cases, 2.3 days (Table 1).

It is interesting to note that there were 19 patients in the series who had been previously treated with, and resistant to, one or more of the following drugs: sulfanilamide, benzyl sulfanilamide, sulfanilyl-sulfanilamide, neo-prontosil and p-amino-benzene-sulfonamido-d-camphor sulfonate. Of these, 13 (68.4%) were cured with sulfapyridine (Table 2).

TABLE 2.—SULFANILAMIDE GROUP RESISTANT CASES.

	No. of patients.	Cures with sulfapyridine.	
		No.	%.
Total series	19	13	68.4
Acute urethritis	13	8	61.0
Subacute urethritis	2	2	100.0
Chronic urethritis	4	3	75.0

Complications. During the course of treatment there occurred 1 case of unilateral epididymitis, 1 of bilateral epididymitis and 2 of gonorrheal arthritis. All of these patients were treatment failures. Of particular interest, we believe, are the 2 cases of arthritis, a greater ratio than we have seen in routine or previous chemotherapeutic treatment of gonorrhea. Both of these were later cured, 1 following treatment with the Kettering hypertherm* and the other following a second course of sulfapyridine.

The patients with inguinal adenitis, unilateral epididymitis and gonorrheal arthritis present before sulfapyridine therapy were all cured. Of the 3 patients with bilateral epididymitis only 1 was cured. In the remaining 2 cases the onset of toxic reactions necessitated withdrawal of the drug before a complete course of the drug had been given.

Toxicity. Forty-five patients (56.2%) had one or more toxic reactions, of which 11 (13.9%) were classified as severe. Among the 50 patients classified as cured, 27 (54%) had some toxic reaction, while in the group of 13 failures a higher incidence was noted, 10 (76.9%) showing untoward reactions (Table 3).

TABLE 3.—TOXIC REACTIONS FROM SULFAPYRIDINE.

	No. of patients.	Total reactions.		Severe reactions.	
		No.	%.	No.	%.
Total series	80	45	56.2	11	13.9
Cures	50	27	54.0	4	8.0
Acute urethritis	42	24	57.1	3	7.3
Subacute urethritis	5	3	60.0	1	20.0
Chronic urethritis	3	0	..	0	
Failures	13	10	76.9	6	46.0
Defaulters	17	8	47.0	0	

The mild toxic reactions following administration of sulfapyridine were headache, nausea, apathy, weakness, dizziness, nervousness, substernal discomfort, pruritus and myalgia. The more severe reactions seen were pyrexia, vomiting, morbiliform rash, generalized hyperemia, polyarthritis, chills, and leukopenia (Table 4). Because these patients were ambulatory, it was thought advisable in the presence of the more severe reactions to stop the administration of sulfapyridine.

There was a general tendency toward leukopenia noted in the majority of cases. In 2 patients the white blood count during treatment was reported to be 3000 and the drug was stopped, although in neither case was there evidence of agranulocytosis. It may be well to note that we have observed no gross hematuria or symptoms of renal colic during the administration of the sulfapyridine in the above prescribed dosage. In 7 of our patients there was a definite pyrexia. This is a higher incidence than was reported by one of us[9] in a series of 400 cases of pneumococcal pneumonia treated with

* Courtesy of Dr. F. Fetter, Philadelphia General Hospital.

sulfapyridine, in which the diagnosis of drug fever was only made twice. This may be due to the fact that the gonorrheal cases were ambulatory and although given smaller dosage, were treated for a longer time.

TABLE 4.—VARIETY OF TOXIC REACTIONS.

	No.
Headache	35
Nausea	23
Apathy	9
Weakness	7
Pyrexia	7
Dizziness	5
Vomiting	4
Morbiliform rash	3
Nervousness	3
Insomnia	2
Confusion	1
Chills	2
Leukopenia	2
Hyperemia	1
Polyarthritis and edema	1
Pruritis	2
Substernal discomfort	2
Myalgia	1

It is interesting to note that 51.1% of the patients who suffered mild reactions and 70% of those developing the more severe symptoms of toxicity had had administered to them previously one or more of the sulfanilamide group of drugs above mentioned (Table 5). All of the toxic reactions rapidly subsided on withdrawal of the drug and a large fluid intake by mouth.

TABLE 5.—PATIENTS WITH TOXIC REACTIONS WHO HAD PREVIOUS TREATMENT WITH SULFANILAMIDE GROUP DRUGS.

	No. of patients.	Percentage of patients.
Among all patients showing reactions	22	51.1
Among patients showing severe reactions	7	70.0

Blood Sulfapyridine Level. We have found no significant difference between the average blood levels of sulfapyridine in the cures and failures, the former being 2.8 mg. per 100 cc. of blood and the latter 2.3 mg. Although those patients with subacute urethritis had an average blood sulfapyridine level of 5.1 mg. per 100 cc. the percentage of patients having untoward reactions is not much greater than that of the patients with acute urethritis whose average blood sulfapyridine level was 2.5 mg. The patients with chronic urethritis, who showed no toxicity, had an average blood sulfapyridine level of 2.6 mg. per 100 cc. (Table 3). Nor was there found a significant variation between the average blood sulfapyridine levels and those patients with mild reactions which was 3.1 mg. per 100 cc., and those with severe reactions which was 3.5 mg. The only excep-

tion to this was 1 patient with a blood sulfapyridine level of 9.3 mg. per 100 cc., who developed a diffuse morbiliform rash and leukopenia.

Discussion of Failures. Among the patients classed as failures were 6 in whom the administration of sulfapyridine was stopped because of severe reactions before a complete course of the drug had been taken. Of these, 1 was cured by a second course of sulfapyridine without the reappearance of toxicity, but does not appear in our statistics as a cure. Four patients of this group were later cured following a short regimen of local therapy, the total time involved being less than might be expected if local therapy alone had been used. The remaining patient was a truant and still had gonorrhea when last seen.

One patient was not only a failure after prolonged treatment with sulfapyridine, but developed gonorrheal arthritis while under treatment, he being the one exception to the 2 weeks' rule of therapy. He was later cured by hyperthermia. The other patient who developed gonorrheal arthritis and who was a failure on one course of sulfapyridine was cured by a second course with a maximum dose of of 2 gm. per day. There were 2 patients in whom there were no apparent benefits seen but who were cured subsequently with a short course of local therapy. Another showed improvement but defaulted after sulfapyridine was stopped.

The remaining 2 patients who were failures illustrate the value of the complete schedule of the tests of cure. One passed all of the tests of cure except the culture which was returned as positive 1 month after cessation of therapy. The other patient, following a negative first culture, had a recurrent slight morning discharge after the passage of bougies and a second culture was positive 5 weeks after the cessation of therapy. In neither of these cases was there obtained a history of re-exposure to gonorrhea.

Discussion of Defaulters. A review of those patients who either failed to complete their course of treatment or failed to complete the tests of cure reveals some interesting points. In this category are 17 (21%) patients of whom 12 were negro and 5 were white. In out-patient department work of this character a certain number of patients default. This is particularly true at the present time, when so many transients are wandering from city to city in search of work. Three patients visited the clinic once only, 3 had only two visits and no surmises can be drawn about them. One patient completed almost his entire course of therapy without much improvement and was a probable failure. Another also had completed almost the entire prescribed course but his urine which had become clear was hazy on his last visit. However, the remaining 9 patients were all probable cures, their urine having been clear for from 3 to 10 days. One of these had had all of the tests of cure but did not return for follow up, and another had had the passage of bougies without

recurrence of discharge or pus in the urine when last seen. Eliminating the patients who were seen on only 1 or 2 occasions, there was then 81.8% of probable cures in this group of patients who defaulted.

TABLE 6.—COMPARATIVE RESULTS IN THE TREATMENT OF GONORRHEAL URETHRITIS IN THE MALE WITH SULFAPYRIDINE.

	Dosage of sulfapyridine.	Local treatment.	No. of male patients.	Toxicity, %	Disappearance of discharge after treatment.	Successful results, %
McGregor-Robertson, J. G.: Lancet, **2**, 1463, 1938	19 gm. in 7 days	With	100	45.0	4.5	96.0
	21 gm. in 7 days	Without	101	..	3.3	80.0
Lloyd, V. E., Erskine, D., and Johnson, A. G.: Ibid., p. 1160	22.5 gm. in 10 days	With	108	22.0	3.9	85.0
Prebble, E. E.: Ibid., p. 1163	15–60 gm. in 5–12 days	Without	25	5.6		48.0
		With	40			62.5
Bowie, F. J. T., Anderson, T. E., Dawson, A., and Mackay, J. F.: Brit. Med. J., **1**, 711, 1939	Variable; average, 3 gm. per day for 4–5 days, then 1.5 gm. per day for 3–4 days	Without	73	37.0 on aver. dosage		93.0+
		With	24			
Durel, P.: Presse méd., **46**, 1571, 1938	18 gm. in 9 days	Without	73			Acute, 80
						Prolonged 70
Leroy, J.: Ann. d. mal. ven., **33**, 729, 1938	3 gm. per day for 10 days or less	Without	22	30.0		81.8
Batchelor, R. C. L., Lees, R., Murrell, M., and Braine, G. I. H.: Brit. Med. J., **2**, 1142, 1938	3 gm. per day for 5 days then reduced for 7 to 9 days	Without	79	25.3	4.0+	92.4
Girard, Andorino et Jaubert: Ann. d. mal. ven., **34**, 83, 1939	18 gm. in 9 days	Without	20	Slight		100.0
Marinkovitch, R.: Brit. Med. J., **1**, 317, 1939	42 gm. in 21 days	With	50	8.0		86.0
Reyn, A.: Ugesk. f. laeger., **101**, 466, 1939	12.5 gm. in 8–14 days	Without	30	7.0		Acute, 87.0
			10			Chronic, 90.0
Johnson, S. H., Leberman, P., and Pepper, D. S.	3 gm. per day for 4 days, then 2 gm. per day for 6–10 days	Without	76	56.2	2.77	80.3

Comment. A survey of the available literature on the treatment of gonorrhea with sulfapyridine reveals an almost universal opinion that the results obtained with sulfapyridine surpass those obtained with sulfanilamide. This coincides with the results seen in this clinic by 2 or us[6] when under the same conditions as the present study we had only 40.6% of cures with sulfanilamide. None of the four other sulfanilamide derivatives that have been used in this clinic in the treatment of gonorrhea in the male have given as good results as we have seen with the use of sulfapyridine. The results obtained in series of patients that are comparable to ours, by other

writers (Table 6) are in general somewhat better. However, some of the statistical cures are quoted as successful results and the criteria of cure are not always given. If we include the 2 patients in our series who were failures with one course of sulfapyridine and who were cured with a second course of the drug, and the 9 defaulters who were probable cures, we obtained 80.3% of successful results. We have found sulfapyridine to be efficacious in the treatment of gonorrhea that has been resistant to previous therapy with other drugs of the sulfanilamide group. Cokkinis and McElligott[2] advise delay in administering sulfapyridine until the second week of the disease; we, however, have seen no rationale in this delay both from the ultimate results and from the patient's viewpoint. Delay is dangerous from a public health standpoint in the early highly infectious period, it increases the anxiety of the patient because of persistence of symptoms, it brings close the danger period of complications and increases the likelihood of the patients defaulting. Although our dosage scale was approximately average in comparison to that of other authors quoted (Table 6), the incidence of toxicity in our series is higher than in any series we have noted. This may be due to the fact that a particular effort was made each visit, to inquire specifically if any untoward reactions had occurred. The rather high percentage of toxicity (56.2%) is, however, not significantly different from the 55% of untoward reactions that we reported[6] in a series of male patients with gonorrhea treated with sulfanilamide. None of the toxic reactions have resulted in impairment of the patient's health. We do not think that a dose higher than 3 gm. a day is necessary or justified in an ambulatory patient, and this should be reduced to 2 gm. a day or less if toxic reactions are prominent. If sulfapyridine is going to be effective, it will almost invariably be so within the first week of treatment, and we therefore feel that the primary course should not be prolonged over a period of 2 weeks. In view of the two favorable results following a subsequent course of the drug, it is thought that the use of repeated courses of sulfapyridine is worthy of further trial. From our experience with blood sulfapyridine levels in this series of patients, we have decided that they are of no value as we have not been able to correlate the blood level with either the incidence of toxic reaction or the clinical response to the drug.

Summary. 1. Sixty-three of 80 male patients with gonorrheal urethritis, treated with sulfapyridine, were adequately followed.

2. Of these 63 patients, 50 (79.2%) passed all the tests of cure, the average duration of discharge in these cases being 2.77 days.

3. The dosage schedule was 3 gm. of sulfapyridine a day for 4 days, then 2 gm. a day for 6 to 10 days.

4. In a group of 19 patients resistant to previous treatment with a sulfanilamide derivative, 68.4% were cures with sulfapyridine thereafter.

5. Forty-five patients (56.2%) had one or more toxic reactions.

6. Blood sulfapyridine levels were of no significance in prophesying reactions or cures.

Conclusion. In our experience, sulfapyridine has been the most efficient sulfanilamide derivative in the treatment of gonococcal urethritis in the male.

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THE ELIMINATION OF THE EFFECT OF THE CHEMICAL MEDIATOR OF RENAL HYPERTENSION.* †

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Hypertension of renal ischemic origin, according to our previous results,[7,13,14] appears to depend upon the ratio of ischemic to normal kidney substance. For example, the removal of the normal kidney in normotensive dogs with unilateral renal ischemia results in a reappearance or intensification of the hypertension. These observations might have been due to an increase in the load of the remaining kidney aggravating its relative ischemia rather than to the removal of any counteraction on the part of the normal kidney. We have, therefore, subjected this concept to further study by noting whether or not the presence of a normal kidney had any effect on the dissipation of the hypertension following removal of the ischemic kidney.

Method. For this purpose, the results of two types of nephrectomies in hypertensive animals were compared: *a*, when the ischemic kidney responsible for the hypertension was removed leaving the normal kidney *in situ;* and, *b*, when a total nephrectomy was done. As controls, the blood pressure changes in normotensive animals were followed after unilateral or bilateral nephrectomy.

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† A preliminary report was presented to the Central Society for Clinical Research, Chicago, November, 1938.

All blood pressure determinations were made without anesthesia using the Hamilton needle manometer technique,[10] which gives accurate systolic and diastolic pressures. All the operations were done aseptically, the renal clamps being applied under nembutal anesthesia, and the nephrectomies under ether. Only trained dogs were used. The period of training was considered completed when the diastolic blood pressure on at least three successive readings was found to be constant within ±5 mm. Hg. After a satisfactory control period was obtained, these animals were subjected to unilateral or bilateral renal ischemia using the Goldblatt technique.[9] Some days after hypertension had developed, the appropriate nephrectomy was done and hourly determinations of blood pressure values were made to determine how soon the normal blood pressure was reached. The time selected as the end point of the hypertensive period was that when the diastolic pressure first reached within 5 mm. Hg of the normal control pressure level. Zero time was considered to be the time during the operation when the blood supply of the kidney to be removed was occluded. In this regard, we have found that the systolic pressure is much more variable than the diastolic, especially with heart rate changes, and is therefore unsuitable for studies such as ours. This criticism also holds in the case of mean pressure which is affected by the systolic pressure. We have relied upon the diastolic pressure in our analysis since we have found this a more satisfactory criterion.

Discussion of Results. The lag in the return of the arterial pressure to normal following removal of the ischemic kidney is shown in Figures 1 and 2. The former shows the results (range and mean) when a normal kidney was left *in situ*, the latter, when no kidney remained. A typical experiment with both types of nephrectomy, is shown in Figure 3. It is apparent from these figures that a definite difference exists in the time at which hypertension disappears following removal of the ischemic kidney, depending on whether or not a normal kidney is left *in situ*. In the 6 experiments in which the ischemic kidney was removed and a normal kidney left intact, the hypertension disappeared and the normal pressure level was reached in 6, 6, 4, 4½, 3½ and 4½ hours respectively, an average of 5 hours. In these animals, the ischemia had been induced by renal clamping 16, 5, 28, 10, 10 and 18 days respectively prior to the nephrectomy.

In the 7 experiments in which the remaining kidney or both kidneys were removed (total nephrectomy) in hypertensive dogs, the hypertension following the operation lasted longer; the blood pressure in these dogs remained above the normal control level for 50+, 10½+, between 12½ and 21, 9, 13, 40 and 15 hours respectively. In these animals, the renal clamping leading to hypertension was done 116, 27, 11, 24, 2, 13 and 2 days respectively prior to the nephrectomy. Thus, the presence of a normal kidney reduced the duration of the hypertension following removal of the ischemic kidney, and this occurred despite the fact that in the absence of both kidneys, the animals were subject to the depressor action which accompanies the development of uremia. This difference is not related to the duration of the hypertension previous to nephrec-

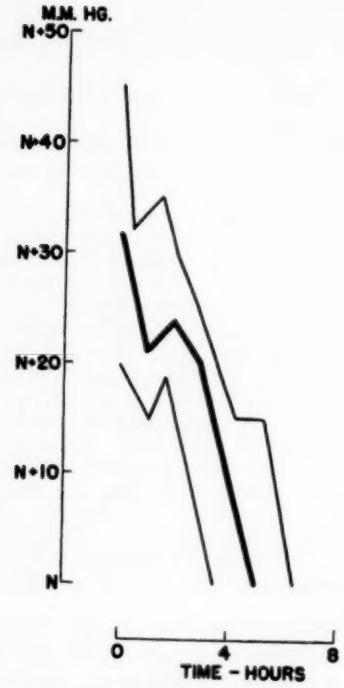

FIG. 1.—The rate of dissipation of hypertension in 6 experiments following removal of the ischemic kidney leaving a normal kidney *in situ*. Zero time is the time during the operation when the blood supply to the kidney(s) to be removed is occluded, ordinates show the diastolic pressure readings above the control level (*N*) in mm. Hg. The light lines show the range and the heavy line shows the mean diastolic pressures. Discussed in text.

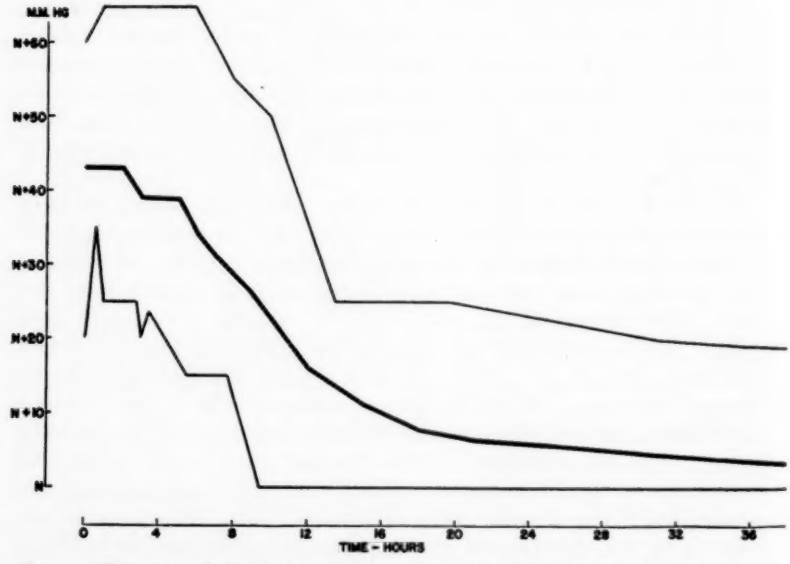

FIG. 2.—The rate of dissipation of hypertension in 7 experiments following total nephrectomy. Conventions as in Figure 1. Discussed in text.

tomy as this duration was of the same order in both groups. On the average, the blood pressure remained above the normal control

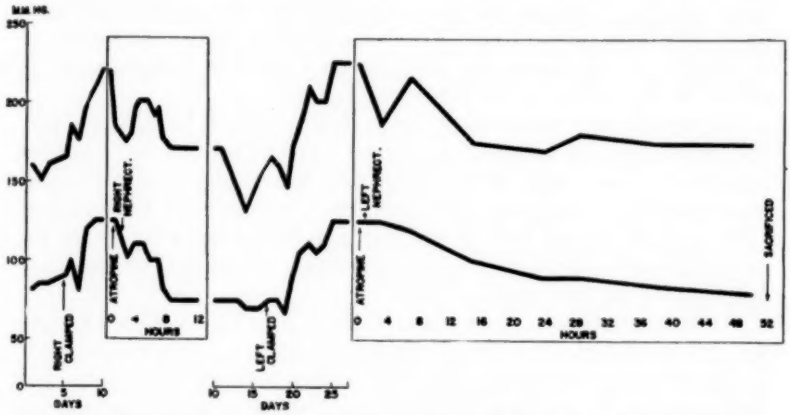

FIG. 3.—Complete protocol of a single experiment typical of all to show difference in rate of dissipation of hypertension, depending on whether or not a normal kidney was left *in situ*. Lower line is diastolic, upper, systolic blood pressure obtained from femoral artery. Note that in the frames the time scale is changed to hours instead of days. Indicated on chart are time when renal arteries were clamped and of right and left nephrectomies.

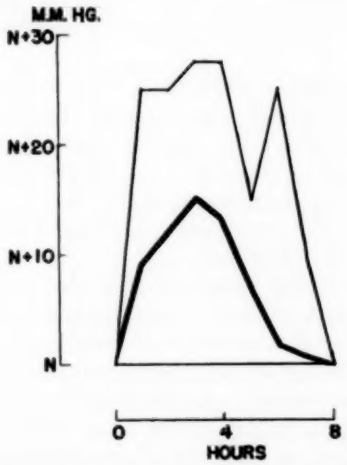

FIG. 4.—The development of a transitory neurogenic hypertension following unilateral or bilateral nephrectomy in 14 normotensive dogs. Conventions as in Figure 1. Discussed in text

level for about 28 hours after total nephrectomy, roughly 5 times longer than when a normal kidney was left in place.

It is possible that when a normal kidney remained *in situ* the lag

might have been even less than we found, since a transitory postoperative hypertension lasting about 6 hours was frequently found in normotensive animals subjected to unilateral or bilateral nephrectomy (*cf.* 13). Our experience on this point to date with 8 unilateral and 6 bilateral nephrectomies in normotensive dogs is summarized in Figure 4. Evidence for the presence of this complication is shown in the hump in the curves of Figure 1.

Our results are not in accord with those reported by Dicker,[5] but the significance of his results may be vitiated by the fact that he apparently took only single daily pressure readings and utilized mean pressure variations. Furthermore, the results of Blalock and Levy and of Verney and Vogt[18] are not in accord with his as regards the persistence of the hypertension. Goldblatt's[8a] data are not detailed on this point.

While inspection of the data of Blalock and Levy[2] show changes which accord with ours, the sharp differentiation which we obtained is not shown in their data. The difference between our results and theirs cannot be ascribed to the general anesthesia we used during the nephrectomy operation, since we have found that ether anesthesia in normotensive dogs subjected to a mock operation does not alter the blood pressure in the postoperative period with which we are concerned.[13] It must be due to the use of the more variable mean pressure in their experiments.

Interpretation of Results. It is evident that our present results indicate that the presence and intensity of hypertension is dependent upon the ratio:

$$\frac{\text{Amount of ischemic kidney tissue}}{\text{Amount of normal kidney tissue}}$$

This is in accord with our previous data and is supported by the recent work of Fasciolo, Houssay and Taquini,[6] who showed that hypertension following homotransplantation of ischemic kidney is more intense in the dog previously subjected to complete nephrectomy than in the normal animal.

Our results give added weight to the thesis that hypertension due to renal ischemia is mediated by a humoral mechanism. They indicate that the chemical mediator of renal hypertension is rapidly destroyed, neutralized or otherwise eliminated when normal kidney tissue remains in the animal. In the absence of normal renal tissue, however, this process cannot occur at a rapid rate. The rapid fall in blood pressure on removal of the ischemic kidney when a normal kidney is left *in situ* leads us to the view that an equilibrium in production, on the one hand, and neutralization, destruction or elimination of the chemical mediator, on the other, has been established during the maintenance of the hypertension. Removal of the source of the chemical mediator, the ischemic kidney, upsets the equilibrium and results in a rapid elimination of the effects of the substance.

The difference in the persistence of hypertension favors the view that renin is somehow related to renal hypertension since Tigerstedt and Bergman[17] showed in work since confirmed that the injection of an extract of the kidney (renin) caused a more pronounced rise in blood pressure in nephrectomized than in normal rabbits. Our results further indicate that substances which are rapidly destroyed by the extrarenal tissues can be eliminated as possible pressor factors in this form of hypertension.

Our results with nephrectomy are in line with previous work[5,8b,9,12] in pointing to the fact that hypertension of renal ischemic origin is not due to the retention of products of tissue activity in the absence of renal excretion. However, this does not rule out the possibility that the hypertension may be due to the retention of such products of normal or ischemic kidney activity, for in complete nephrectomy, we not only remove the excretory function, but also the metabolic processes peculiar to the kidney.

The reversibility of the hypertension of short standing present in our experiments indicates that no irreversible vascular changes had yet been produced, otherwise the effects of the chemical mediator of renal hypertension would not have been so quickly eliminated. Whether a similar reversibility exists in long-standing hypertension demands further investigation.

Analysis of our experiments indicates that the maintenance of the blood pressure of the dog at a normal level does not require the presence of the kidneys. By contrast the hypertensive level following renal ischemia appears to involve the kidneys not only in its creation and maintenance, but also in its elimination. This difference in the normotensive and hypertensive mechanisms is shown in our bilaterally nephrectomized hypertensive dogs by the fact that after the blood pressure had returned to the normal diastolic level, it was maintained there until shortly before death. This sharp differentiation between the two stages in blood pressure fall points to the independent origin of the normotensive and hypertensive states. This is further supported by the fact that in normotensive dogs complete nephrectomy causes only the second preagonal fall. These facts apply, of course, only if shock and early uremia are ruled out.

These results have a hearing on clinical studies. Twenty years ago O'Conor[16] reported that the drainage of the bladder by suprapubic cystotomy in cases of urinary retention following prostatic obstruction caused an appreciable drop in blood pressure within 24 hours in 41 out of 55 cases. The greater drops occurred in cases with marked hypertension. This observation has been subsequently confirmed. Since a number of investigators[5,11,12] have found no essential differences in hypertension due to experimental occlusion of the ureter, extreme distention of the bladder and the experimental Goldblatt variety, it is easy to assume that these hypertensions are

due to the same mechanism: renal ischemia. In relieving the bladder distention, therefore, the renal ischemia was presumably relieved and the kidneys then caused the prompt drop in blood pressure just as occurs in the dog when the ischemic kidney is removed and the normal kidney is left *in situ*.

Actual removal of the ischemic kidney in human beings has been recently reported. Butler[4] has reported a case in which removal of a pyuric kidney resulted in a return to normal pressure within one day. Barker and Waltman[1] have reported a prompt return of pressure to normal in several cases following removal of a hydronephrotic kidney. Leadbetter and Burkland[15] noted an "immediate" decline in both systolic and diastolic pressures following removal of an ectopic ischemic kidney having its main renal artery partly occluded. Boyd and Lewis[3] noted that the pressure fell "immediately" to normal after removing an infarcted kidney. Unfortunately, the hourly changes in blood pressure in these cases are not given. It would be valuable to determine whether a neurogenic rise occurs immediately after nephrectomy in man (there was such a rise in one of Barker's cases 3 hours postoperatively). It may also be of value to determine whether the time course in such patients compares with that in the experimental animal. In view of our results, it is not impossible that the time course of the return of the pressure to normal levels will help to indicate whether or not the remaining kidney is severely damaged.

Summary. 1. Removal of the ischemic kidney in hypertensive dogs with a normal kidney remaining *in situ* results in a return to normotensive levels within 6 hours. The time period for this return might have been prolonged because of interference by the fleeting neurogenic hypertension which often follows nephrectomy.

2. Removal of the ischemic kidney in hypertensive dogs with no kidney remaining results in a considerably slower return to the normal pressure levels, averaging in our series five times that found when a normal kidney was left *in situ*.

3. These results suggest that the chemical mediator of hypertension due to renal ischemia is destroyed, neutralized or otherwise eliminated at a rapid rate only in the presence of normal kidney tissue.

4. Our results indicate that normotension is independent of renal action, while renal hypertension depends upon the kidney for its genesis, continuation and elimination.

We are indebted to Miss L. Friedberg for her assistance in carrying out these experiments.

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THE RESPONSE IN BLOOD PRESSURE OF HYPERTENSIVE PATIENTS TO ACETYL-BETA-METHYLCHOLINE.*

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The search for the causes of arterial hypertension in man has led to the point where it may be said that high blood pressure is the result of an increased peripheral vascular tone.[16,17,20a] The causes of the increased vascular tone are still uncertain. The sympathetic vasoconstrictor nerves have been relegated to only a contributory rôle. Search for humoral pressor substances is yet in progress and has received new impetus from a method of creating an experimental renal hypertension in animals.

There are those who already speak of an "intrinsic hypertonus of the blood-vessels," independent of any of the known mechanisms for the regulation of vascular tone. However, it is logical to assume that before investigators can speak with conviction of an intrinsic hypertonus of the blood-vessels, they must make certain that all the physiologic mechanisms contributing to the regulation of vascular tone can be exonerated as a cause of hypertension.

In this regard, we question whether the vasodilator mechanisms have been thoroughly investigated in relation to the possibility that a failing vasodilator mechanism might be a factor in the production of arterial hypertension.

The physiologic vasodilator substances of recognized importance are the metabolites of muscle contraction, histamine, and acetylcholine. It has been found that the blood-vessels of hypertensive patients respond normally to the action of the metabolites that accumulate during a period of circulatory arrest,[16,17] so that there

* Abridgment of thesis submitted by Dr. Engle to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

seems to be no reason to suspect a causal relationship of these metabolites to hypertension. Likewise, hypertensive subjects have been reported to exhibit normal vascular reactions to the subcutaneous administration of histamine.[16] A comparison of the vascular reactions of hypertensive and normal individuals to acetylcholine has not been reported.

The physiologic importance of acetylcholine has only in the past decade begun to be appreciated in its rôle of a chemical transmitter of nerve impulses.[1,15] It is now believed that nerve impulses, passing over certain nerves, cause the release at those nerve-endings of acetylcholine. It has been found that a single nerve impulse causes the release of a definite quantity of acetylcholine[6] and it is assumed that variations in the tonic effect of the nerve upon its effector organ are accomplished by changes in the frequency of the nerve impulses travelling over the nerve and the alterations thus produced in the concentration of acetylcholine at the nerve-endings. The concentration of acetylcholine at the nerve-endings is also influenced by an esterase within the tissue fluids which constantly destroys acetylcholine. It is further known that the effect of the nerve impulse is due solely to the acetylcholine present at the nerve-endings, and that this effect can be mimicked by the administration of acetylcholine.[1,10,11] Experimental evidence supports the belief that administered acetylcholine affects only those effector cells that are innervated by the so-called cholinergic nerves.

Generally speaking, the autonomic nervous system exerts its control over vital processes of the body by means of dual mechanisms, one having an inhibitory function and the other having an excitatory function. The autonomic control over the cardiovascular system is no exception. The excitatory influence is mediated by the sympathetic vasoconstrictor and cardiac accelerator nerves, which liberate at their nerve-endings an adrenalin-like substance called "sympathin E."[2] The inhibitory influence is exerted by the nerves which liberate acetylcholine. This dual control over the heart rate has been investigated in detail by Rosenblueth and Simeone.[19] However, the possibility of the existence of a similar dual nervous control over peripheral vascular tone is much less evident. Vasodilator nerves have usually been regarded as unimportant, chiefly because it is known that nearly all the measurable vascular reactions to cooling or warming the body, to pain and to other external stimuli, are mediated largely through the sympathetic vasoconstrictor nerves. However, it seems possible that vasodilator nerves may exert a restraining influence on vascular reactions, and that they may help to maintain a basal vascular tone upon which the activity of the sympathetic vasoconstrictor nerves are superimposed.

It is important to note that vasodilator nerves are distributed throughout the body. Of particular interest are those in the posterior spinal nerve roots because they are unaffected by sympathectomy;

and in the experimental animal they are known to be in constant tone and also to possess central reflex connections.[8,18] Their presence in man has been demonstrated[7] but there is little direct evidence relating to the extent of their influence on peripheral vascular tone. Evidence favors the opinion that they are cholinergic.[21a,b] This does not mean that atropine abolishes their effect, because oddly enough, it does not.[10] However, the effect of stimulating the vasodilator nerves in the posterior roots is enhanced by eserine.[21b]

On the basis of these considerations, we wished to administer acetylcholine to hypertensive patients and to compare the responses in blood pressure to those of normal controls. We reasoned that if in hypertensive individuals the blood-vessels were insensitive to acetylcholine, or were protected from it by some atropine-like substance, we might expect to obtain a subnormal response. We further reasoned that a hyper-response on the part of hypertensive individuals might be the result of a subnormal concentration of acetylcholine around the peripheral blood-vessels, because it is an established fact that after the section and degeneration of the cholinergic nerve supply to a part of the body, that part exhibits a marked sensitivity to the effects of acetylcholine.[1,4,5] Furthermore, if the blood-vessels of hypertensive individuals do respond excessively to acetylcholine, it seems reasonable to postulate that a diminished function of the cholinergic vasodilator nerves is present; otherwise, we should expect a marked peripheral vasodilation to obtain in the hypertensive subject, whereas we believe that quite the opposite condition, a generalized peripheral vasoconstriction, exists.

In conducting our studies we substituted for acetylcholine one of its derivatives, acetyl-beta-methylcholine (mecholyl, Merck).* It seemed desirable to make this substitution because the latter is more stable both in solution and in the body than the former, permitting the investigator to measure more accurately the minor effects resulting from the administration of small doses of the drug. This substitution seemed permissible on the ground that the peripheral action of both drugs is qualitatively the same in the cases of both experimental animals and normal[3,20b] human beings, and on the grounds that the effects of both drugs are similarly altered by the presence of atropine or esserine.[13,14] It would seem, therefore, that the action of both drugs is dependent upon the same physiologic mechanism, and that we might expect that an individual would react similarly to either drug.

We administered acetyl-beta-methylcholine in 2.5 mg. doses subcutaneously to normal individuals (Table 1) and found that it produced little or no decrease in blood pressure. Other investigators have reported that dosages up to 5 mg. usually produce a slight

* We are indebted to Merck & Co. for the acetyl-beta-methylcholine (mecholyl) used in making these observations.

TABLE 1.—NORMAL INDIVIDUALS: RESPONSE TO MECHOLYL, 2.5 MG., SUBCUTANEOUSLY.

Case.	Sex.	Age, Yrs.	Resting B. P.	Lowest B. P. after mecholyl.	Percentile decrease.* Systolic.	Percentile decrease.* Diastolic.
41	F	28	104/58	94/56	9.6	3.4
42	M	29	100/72	92/66	8.0	8.3
43	M	28	100/68	94/64	6.0	5.9
44	F	28	100/64	88/60	12.0	6.2
45	M	30	116/78	110/76	5.2	2.6
46	M	29	100/74	96/68	4.0	8.1
47	F	25	102/56	96/54	5.9	3.6
48	M	30	120/82	116/80	3.3	2.4

* Pressure after mecholyl compared with resting pressure.

TABLE 2.—HYPERTENSIVE PATIENTS: RESPONSE TO MECHOLYL, 2.5 MG., SUBCUTANEOUSLY.

Case.	Sex.	Age, Yrs.	Weight, pounds.	B. P. in consultant's office.	Resting B. P. in hospital.	Lowest B. P. after mecholyl.	Percentile decrease.* Systolic.	Percentile decrease.* Diastolic.
Diffuse Arterial Disease, Group 1.								
33	M	25	149	130/78	130/66	90/40	30.8	39.4
Diffuse Arterial Disease, Group 2.								
1	F	65	168	230/130	156/89	128/70	17.9	21.3
2	F	40	132	180/110	174/112	134/74	23.0	35.5
3	F	42	148	210/110	180/108	132/78	26.6	27.7
5	F	49	125	230/130	160/98	142/84	12.5	14.3
6	F	59	131	170/100	110/60	86/48	21.8	20.0
7	F	41	118	200/130	164/106	120/76	26.8	24.0
9	M	35	155	164/90	146/80	124/64	15.1	20.0
10	F	38	118	190/120	180/118	140/88	22.2	24.1
11	M	41	165	216/140	158/108	130/84	17.6	22.2
15	F	54	140	176/104	138/80	110/62	20.3	22.5
16	F	46	139	220/110	170/100	144/74	15.3	26.0
19	M	33	162	210/130	156/112	138/80	11.5	27.3
22	F	31	105	220/120	174/110	162/90	7.0	18.2
24†	M	38	193	180/120	170/108	162/110		
25	F	60	155	214/120	140/80	130/68	7.1	15.0
27	M	45	154	165/100	130/84	104/74	20.0	11.9
29	F	60	141	220/114	174/86	130/68	25.4	20.9
30	F	36	135	220/120	144/104	124/64	13.9	38.4
31	F	41	154	168/114	120/90	104/74	13.3	18.8
Diffuse Arterial Disease, Group 3.								
4	M	27	148	200/145	200/140	166/114	17.0	18.6
8	M	54	167	210/130	180/120	160/100	11.1	15.3
12	M	36	206	205/130	184/146	160/116	13.0	20.5
18	F	30	126	190/120	158/120	120/90	24.1	25.0
17	M	40	134	208/130	190/118	174/90	8.4	25.0
34	F	34	120	216/140	194/132	146/92	27.4	30.3
Chronic Glomerulonephritis.								
13	M	24	140	160/100	168/106	128/64	23.8	37.4
14	M	46	203	170/110	128/88	110/72	14.1	18.2
20	M	63	176	192/104	164/96	134/80	18.3	16.6
21	F	19	115	144/90	134/62	116/38	13.4	38.7
26	M	56	150	190/100	154/80	136/68	11.7	15.0
28	M	28	...	...	154/96	130/64	15.6	33.3
32	M	28	140	190/126	186/126	166/100	10.8	20.6

* Pressure after mecholyl compared with resting pressure.
† See text.

increase in the blood pressure of the normal human being.[13] In either case, the effect is slight.

In the same manner, we administered acetyl-beta-methylcholine to hypertensive patients (Table 2). These were all patients who had been hospitalized for study. Their diagnoses included Groups 1, 2, and 3 of essential hypertension,[12] and hypertension associated with chronic nephritis and pyelonephritis. The results of this comparison are given in Tables 1 and 2. In nearly all instances, there was a moderate to marked decrease in blood pressure. The absolute decrease in blood pressure was many times normal, and the percentile decrease in blood pressure averaged three to four times that which characterized the normal individuals. In some instances, the diastolic pressure of the hypertensive subjects decreased to well below the normal level. There was usually an increase in pulse rate roughly proportional to the decrease in blood pressure.

Two observations seemed to indicate that the hyper-response to acetyl-beta-methylcholine might be related to the physiologic basis for the hypertension. There were 6 patients whose blood pressures, under resting conditions, had decreased to normal at the time our observations were made. These, none the less, experienced a definitely greater percentile decrease in blood pressure than did the non-hypertensive individuals. It therefore seems clear that the greater percentile decrease in blood pressure is independent of a high primary level of blood pressure and is probably related to the hypertensive disease. Another patient, whose diagnosis seemed to belong to the ordinary Group 2 of essential hypertension (Table 2, Case 24), on two separate occasions experienced no significant changes in blood pressure in response to the drug. We wonder if the hypertension of that individual rests upon a different physiologic basis than the hypertension of the other patients so tested.

TABLE 3.—HYPERTENSIVE PATIENTS: EFFECT OF MECHOLYL, 2.5 MG., SUBCUTANEOUSLY ON COLD PRESSOR RESPONSE.

Case.	Sex.	Age.	Resting B. P.	Highest B.P. during cold test.	Lowest B. P. after mecholyl.	Highest B.P. during cold test after mecholyl.
27	M	45	124/76	148/128	104/70	126/102
28	M	28	160/80	202/130	130/60	182/80
29	F	60	182/90	208/100	130/68	152/74
31	F	41	134/90	150/110	114/66	114/70
32	M	28	196/130	204/140	164/114	180/124
34	F	34	184/130	226/180	146/92	184/124

Since the sudden and often abnormal elevation of blood pressure, which is usually experienced by hypertensive subjects in response to placing the hand in ice-water, is thought to be the result of a generalized reflex vasoconstriction, we have tested the effect of acetyl-beta-methylcholine upon this response. After having patients perform the cold water test in the usual manner and allowing sufficient time for the blood pressure to return to the control level, we

administered 2.5 mg. of the drug. As soon as a considerable decrease in blood pressure had occurred, we repeated the cold test and compared the result of the second test to that of the first. The results of our observations are given in Table 3. In every instance the reflex vasoconstrictor response of hypertensive patients to cold was markedly reduced after administering acetyl-beta-methylcholine.

The decrease in blood pressure and the abolition of the vasoconstrictor response to the cold test that occurs during general anesthesia are thought to be caused largely by a maximal diminution of the nervous control over the blood-vessels, including a nearly complete diminution of the nervous vasoconstrictor influence. We have compared the decrease in the blood pressure of hypertensive patients during anesthesia induced by the intravenous injection of pentothal sodium to that occurring after the subcutaneous administration of 2.5 mg. of acetyl-beta-methylcholine. The results of our observations are given in Table 4. In every instance, the subcutaneous administration of acetyl-beta-methylcholine in a dose that scarcely affected the level of blood pressure of a normal subject, caused a decrease in the blood pressure of hypertensive patients to a lower reading than that resulting from deep anesthesia, induced by the administration of pentothal sodium.

TABLE 4.—HYPERTENSIVE PATIENTS: A COMPARISON OF THE FALL IN BLOOD PRESSURE RESULTING FROM INTRAVENOUS ANESTHESIA (PENTOTHAL SODIUM) TO THAT RESULTING FROM THE SUBCUTANEOUS ADMINISTRATION OF MECHOLYL, 2.5 MG.

Case.	Resting B. P.	Lowest B. P. during anesthesia.	Resting B. P.	Lowest B. P. after mecholyl.	Percentile decrease* in diastolic B.P.	
					Anesthesia.	Mecholyl.
3	230/140	134/98	180/108	132/78	30.0	27.8
7	214/126	160/114	164/106	120/76	9.5	28.3
4	206/140	160/124	200/140	166/114	11.4	18.6
11	176/126	154/110	158/108	130/84	12.7	22.2
16	224/120	150/80	170/100	144/74	33.3	26.0
18	170/120	138/106	158/120	120/90	11.7	25.0
19	188/124	140/110	156/112	138/80	11.3	28.6
30	154/98	140/98	144/104	124/64	0	38.5
32	160/110	144/110	186/126	166/100	0	20.6
34	208/142	160/124	194/132	146/92	12.7	30.3

* Pressure compared with resting pressure.

We have made a similar comparative study of the blood pressure responses to the intravenous administration of acetyl-beta-methylcholine of both normal dogs and dogs having experimentally induced renal hypertension. The introduction of the Goldblatt method of producing a persistent hypertension in animals has furnished opportunities for the study of experimental hypertension. It has become exceedingly important to know whether this type of hypertension as it affects animals is similar to the common types of hypertension

affecting man. For this reason, it is desirable to undertake any method of comparing the two states.

These observations were made under the direction of Dr. H. E. Essex and Dr. J. F. Herrick at the Institute of Experimental Medicine of The Mayo Foundation. The blood pressures were recorded by the intra-arterial method of Hamilton[9] and associates. The acetyl-beta-methylcholine was administered intravenously in doses small enough to produce less than a 20% decrease in blood pressure, as well as in larger doses to produce up to a 50% decrease, so as to provide a better comparison and to show that the vessels of hypertensive dogs were dilatable. Results of these studies are given in Table 5. It appears from our observations that the percentile decrease in blood pressure in response to the administration of acetyl-beta-methylcholine is no greater in dogs having experimentally induced renal hypertension than it is in normal dogs. In this respect, this type of experimentally induced hypertension seemingly differs from the common types of hypertension which affect man.

TABLE 5.—NORMAL AND HYPERTENSIVE DOGS: RESPONSE TO INTRAVENOUS ADMINISTRATION OF MECHOLYL.

No. of dog.	Weight in kg.	Dose in mg.	Control B. P.	B. P. after mecholyl	Percentile decrease.† Systolic.	Diastolic.
T 437*	12.25	0.0014	261/146	228/120	12.6	17.8
		0.0028	278/151	202/106	27.3	29.8
		0.075	263/142	131/65	50.2	54.2
T 438*	9.5	0.0012	243/119	199/98	18.1	17.6
		0.0024	246/120	179/84	27.2	30.0
		0.060	260/115	124/56	52.3	51.3
T 542‡	18.0	0.002	210/111	173/90	17.6	18.9
		0.004	224/117	148/80	33.9	31.6
		0.1	214/118	99/61	53.7	48.3
T 633‡	21.5	0.002	224/110	144/80	35.7	27.3
		0.004	223/117	134/68	39.9	41.9
		0.1	217/116	102/51	53.0	56.0

* Hypertensive.
† Pressure after mecholyl compared to control pressure.
‡ Normal.

Summary. In summary, we believe that our observations demonstrate almost certainly that the peripheral blood-vessels of most hypertensive patients react by a greater proportional dilatation in response to the administration of acetyl-beta-methylcholine than do the blood-vessels of normal individuals. It is difficult to understand how peripheral blood-vessels which display a hyperdilatation in response to the administration of choline derivatives can be maintained in a state of increased tone in the case of hypertensive individuals, unless we assume that the concentration of acetylcholine at the nerve-endings of the cholinergic vasodilator nerves of these patients is subnormal. We present these observations in support of the hypothesis that a deficient acetylcholine-vasodilator mechanism may be a factor in the production of the arterial

hypertension of man. It would seem that this approach to the study of mechanisms for the production of hypertension deserves further investigation.

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CHRONIC HYPERTROPHIC SPINAL PACHYMENINGITIS.

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Although not an extremely rare condition, chronic hypertrophic spinal pachymeningitis is frequently overlooked in the differential diagnosis of certain spinal cord syndromes. Its diagnosis, though difficult, is important, since the condition is often surgically or medically remediable. Since 1926, when Moniz[15] reviewed the subject from the studies of Charcot,[6] up to 1925, little attention has been given the subject in English or American literature, and most of the foreign articles have consisted of single case reports.

We have collected 15 cases of hypertrophic spinal pachymeningitis (12 with autopsies), and feel that this number affords an opportunity to summarize some of the outstanding clinical and pathologic features of the condition. Moreover, it would perhaps be pertinent here to review briefly some of the current opinions regarding hypertrophic spinal pachymeningitis.

Etiology. Syphilis is generally conceded to outrank other etiological agents,[2,3,24] tuberculosis being next in frequency. Besides these causes, however, the meningitides,[1,2] neighboring or remotely situated, pyogenic and other types of infections are thought to affect the meninges in a similar manner.[4,9,10,13,17,18,26,27] Trauma has been ascribed an etiologic rôle by Pommé *et al.*[19] and Richard *et al.*[21] and was apparently the precipitating cause in 1 of our cases. Pachymeningitis has often been associated with true syringomyelia (occurring in 1 case of our series) but whether a mere associated congenital phenomenon or a cause of the syringomyelia itself by vascular interference is a nice question which is discussed by Moniz.[15] Lorey and Schaltenbrand[14] have raised the question of Roentgen ray irradiation's causing pachymeningitis. Finally, the etiology of certain cases of pachymeningitis has to be ascribed to a "cryptogenic" category.[6,7,19]

Pathology. As its name implies, hypertrophic spinal pachymeningitis is a chronic inflammatory reaction, consisting essentially of a fibrous hyperplasia of the dura often with perivascular and interstitial lymphocytic infiltration. The inner surface of the dura undergoes hyperplasia and sometimes attains 5 to 10 times its normal thickness. The underlying piaärachnoid is usually involved in this process; and the cord, leptomeninges and dura become mutually adherent. Calcium deposition and hyalinization are sometimes observed.[15] The spinal roots are often enmeshed in dense adhesions and may show degenerative changes. The cord itself shows varying degrees of myelomalacia, with demyelination especially of the posterior columns, dorsal and ventral spinocerebellar tracts, while different stages of degeneration are observed in the ganglion cells. Passive congestion and perivascular round-cell infiltration are sometimes observed in the intrinsic vessels of the cord.[18] The degenerative changes are apt to be found in segments considerably above and below the apparent clinical "level;"[15] and, although the disease has a particular affinity for the lower cervical region, any portion of the spinal or intracranial meninges may be affected. Cavity formation in the cord is not infrequently observed, and is generally thought to be due to degenerations secondary to embarrassed blood supply.[15]

Symptomatology and Diagnosis. From a clinical neurologic standpoint, the symptomatology has no pathognomonic features, and may vary from day to day. This variability made some consider hysteria in 2 of our cases. The usual symptoms consist of root pain and atrophy of the muscles with hypoflexia or areflexia in the distribution of the roots and segments involved and with pyramidal tract signs below and not infrequently above this level. The sensory loss may be of a dissociated type. Ataxia was a prominent symptom in our series. Vesical dysfunction is not infrequent.

Ordinary Roentgen rays of the vertebral column reveal nothing

characteristic except in cases of Pott's disease, vertebral trauma, and in certain cases of syringomyelia where associated congenital bony anomalies may be present. The great majority of authors agree, however, that Roentgen studies after lipiodol injection offer possibly the best means of strengthening the diagnosis preoperatively. In the foreign literature the findings are usually described as partial block at the clinical level, with streaking and breaking up of the lipiodol column;[8,15] and with retardation of its passage below the level under suspicion, most of the injections having been into the cisterna magna. This procedure is attended with a certain risk of phrenic paralysis. Siebner[23] has reported on a death occurring 12 hours afterwards.

Spinal manometry and examination of the cerebrospinal fluid are of little help in excluding cord tumor, except that a partial block may be suggestive, and where this is the case in the presence of a positive serology, one is justly suspicious. The total protein content is usually reported as elevated and is regarded as an expression of an inflammatory exudate, local venous stasis with transudation of plasma proteins, stagnation of the fluid below a block or a combination of these factors. Richard, Dechaume and Croizat[21] report a marked decrease in the protein after a decompression in their case. In the more active inflammatory types of the disorder the cell count as well as the protein is apt to be elevated. The colloidal gold curve is usually abnormal but, except in luetic cases, presents no specific picture.

With syphilis and tuberculosis excluded, the chief difficulty is the differentiation from cord tumor. Here Moniz emphasizes the value of lipiodol: 1, Once the lipiodol passes a tumor there is an undelayed "sheer drop" into the sacral cul-de-sac, but in pachymeningitis, consecutive examinations over several days may reveal particles of oil suspended at varying regions below the clinical level; 2, motor symptoms above the level of the lipiodol block argue against tumor; 3, lipiodol produces a transient exacerbation of segmental symptoms in the case of a chronic inflammatory process, while this is much less apt to occur in tumor. Moreover, it is probable that a number of laminectomies have been performed on such cases in the anticipation of finding cord tumor. Several foreign writers have reported their preoperative diagnostic errors in confusing pachymeningitis with neoplasm and we feel a similar humility in stating that the condition was merely "suspected" in only one of our group of 12 autopsied cases.

Treatment. So-called "arachnoiditis," which in certain instances is even a questionable entity, is similar though hardly comparable to hypertrophic spinal pachymeningitis in degree of severity. In the latter condition one is faced with a definitely and progressively thickening dura, and with the prospect sooner or later of a complete transverse myelomalacia. We share the general conviction

FIG. 1 FIG. 2

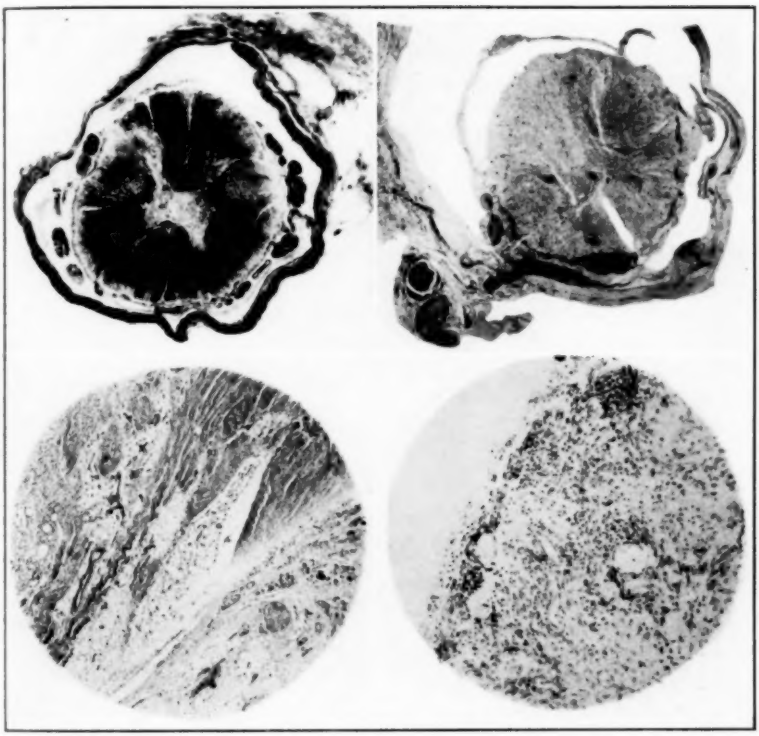

FIG. 3 FIG. 4

HYPERTROPHIC SPINAL PACHYMENINGITIS—N.P. NO. 28–200.

FIG. 1.—Dural thickening. Pyramidal, posterior column, and "rim" demyelination. (Weigert—12x.)

FIG. 2.—Intrinsic congestion and degeneration. Implication of roots in adhesions. (Van Gieson—12x.)

FIG. 3.—Dura: Fibrosis and areas of hyalinization. (H. & E.—27x.)

FIG. 4.—Leptomeninges: Interstitial and perivascular lymphocytic infiltration. Fibroblastic reaction. (Nissl—102x.)

that a rational therapy should be one directed toward the arrest or eradication of the compression of the cord or of its blood supply.

In accord with Capani,[5] we feel that vigorous antiluetic therapy in syphilitic cases merits a clinical trial first. This, however, coulp hardly be expected to accomplish more than an arrest of the pathologic process with possible return of neural functions where irreversible changes had not yet occurred. It is difficult, however, to conceive of any medicinal therapy which would effect the dissolution of a strangulating ring of thickened dura. The recent literature has contained little reference to the treatment of pachymeningitis (as such) of tuberculous etiology.

Most authors agree that laminectomy and splitting the dura for decompression is the therapeutic procedure of choice in the nontuberculous and non-luetic cases. Moreover, Puente, Orlando and Dowling[20] report improvement from such a procedure in a case of heredolues. Crouzon,[7] Joisten,[11] Veraguth,[25] Pommé,[19] Richard *et al.*[21] and others[12,17,22] report both subjective and objective improvement in cases after operative intervention. Knust and Salus, in surveying the literature in 1931, indicate that 10 of 16 cases operated have been either improved or cured.

Method of Study. Correlations of the clinical features of 15 cases of chronic hypertrophic spinal meningitis and of the gross and microscopic pathologic findings on 12 of these cases were tabulated. The diagnosis in 3 instances was clinical; in the remaining 12 cases, however, pathologic, being based on a relatively localized pronounced thickening of the spinal dura to a degree apparently sufficient to account for the clinical signs pointing to this level. Dural thickenings associated with acute inflammation such as pyogenic osteomyelitis were omitted from this study. "Brain symptoms" refers to those cases showing gross mental aberrations, cranial nerve dysfunctions, or both.

TABLE 1.—ETIOLOGIC FEATURES IN CHRONIC HYPERTROPHIC SPINAL PACHYMENINGITIS (15 CASES).

Age range (21 to 65):		
	20–30	4
	30–40	4
	40–50	1
	50–60	4
	60–70	2
Sex:	Female	5
	Male	10
Etiology:	Lues	8
	BWR (alone)	2
	CSF	6
	T.B.	2
	Undetermined	5
	Trauma (?)	1
	Associated with syringomyelia	2

Results. Etiologic factors are presented in Table 1. Table 2 assays a correlation of certain clinical features with the nature and location of the spinal lesions, indicating that clinically the prominence of pain, sensory disturbances, ataxia, pyramidal and lower

motor neuron symptoms, and vesical dysfunction all had adequate pathologic bases. Table 3 correlates the clinical and pathologic diagnosis on the 12 autopsied cases.

TABLE 2.—NUMERICAL CORRELATION OF CLINICAL AND PATHOLOGIC FEATURES OF CHRONIC HYPERTROPHIC SPINAL PACHYMENINGITIS.

Clinical Features (15 Cases). Symptoms.	No. of cases.	*Pathologic Features (12 Cases).* Findings.	No. of cases.
Pain	8	Dura thickened	12
		Piaärach. thickened	10
Sensory disturbance	11	Degen. post. horn cells	11
Sensory(?) disturbance	2	Demyelin. sp. thal. tr.	7
Ataxia	11	Demyelin. post. col.	12
Upper extremities	2	Dors. sp. cerebell.	10
Lower extremities	8	Ventral sp. cerebell.	7
Both upper and lower extremities	1		
Pyramidal	13	Demyel. pyr. tract	8
Vesical dysfunction	9	Demyel. pyr. tract(?)	8
Retention	4		
Incontinence(?)	4		
Unspecified	1		
Lower m. neuron	9	Anterior horn cell degen.	12
Atrophy	5		
Fibrillation	3		
Flaccidity	2		
Only hyporeflexia	2		
Brain symptoms	10	Miscellaneous:	
		Cavitation of cord	4
		Hemorrhage	0
		Thrombosis	1
		Perivascular infiltration of meninges	11

TABLE 3.—CORRELATION OF CLINICAL DIAGNOSES AND PATHOLOGIC FINDINGS IN 12 AUTOPSIED CASES SHOWING CHRONIC HYPERTROPHIC SPINAL PACHYMENINGITIS.

Case No.	Clinical diagnosis.	Pathologic diagnosis.
1. 705*	Incomplete myelitis	Pachymeningitis and syringomyelia
2. 727*	Syringomyelia (non-traumatic)	Pachymeningitis and syringomyelia
3. 23–155	Cerebrospinal syphilis	Generalized hypertr. pachy. and C.S. syphilis
4. 29–310	Syph. meningo-myelitis	Pachymeningitis—mid-thoracic
5. 24–81	Tabo-paresis	Cerebrospinal lues—pachym. cervicalis
6. 28–19†	Myelitis or cord tumor	Hypertrophic pachymeningitis
7. 28–200†	Arachnitis or cord tumor	Pachymeningitis and myelomalacia
8. 30–50	Transverse myelitis	Thickening of thoracic dura with myelomalacia
9. 30–301	Transverse myelitis	Pachymeningitis — lumbar cord — myelomalacia
10. 33–172	Tabo-paresis	Pachymeningitis cord. Pial fibrosis of brain
11. 35–251	C.N.S. lues	Pachymeningitis dorso-lumbar cord. Stenosis of 4th ventricle
12. 36–155	Amytrophic lat. scl.	Meningo - vasc. syph. hypertr. pachy. dorsalis

* Univ. of Penna. cases; remaining cases from Phila. Gen. Hosp.
† Underwent laminectomy (oper. diag.).

Discussion. No symptom or syndrome may be regarded as pathognomonic. In fact, from our case studies, luetic hypertrophic

pachymeningitis, although showing an affinity for the cervical and dorsal regions, cannot often be regarded as an exclusively localized process, but rather as a regional manifestation of a usually more generalized meningovascular syphilis. In 10 of our 15 cases definite brain symptoms were clinically manifest.

In 2 of our cases the clinical picture so closely simulated cord tumor that laminectomies were performed. One of these cases showed partial block and negative serology and the other showed no block, negative spinal fluid Wassermann, but signs of fairly definite level (the blood Wassermann in this case was positive, however). Correlating the clinical and pathologic diagnoses in the 12 cases autopsied, we were impressed by the fact that in only 1 instance was any clinical mention made of pachymeningitis, the clinical diagnoses being "myelitis," "cerebrospinal syphilis," "taboparesis," and in 1 instance a diagnosis of amyotrophic lateral sclerosis was made. The term "myelitis" in these cases, we feel, not only is a pathologic misnomer, but detracts attention from the nature of the process. It also invites an easy but sometimes unjustifiable therapeutic pessimism. The major pathologic process is in the meninges, and cord changes are largely secondary to embarrassed blood supply or direct compression of the roots or rim of the cord. If medical therapy fails, we feel that surgical decompression should be given more serious consideration in such cases.

Summary. 1. The pathologic incidence of chronic spinal hypertrophic pachymeningitis far outranks its clinical detection, the latter being of some importance as the syndrome may simulate cord tumor. Moreover, pachymeningitis itself is not infrequently surgically remediable.

2. A clinical study of 15 cases of chronic hypertrophic spinal pachymeningitis with a pathologic correlation of 12 of these cases is presented.

3. The outstanding clinical features of an "ideal case" appear to be: adult age, male, lues, radicular pain, ill-defined sensory level, ataxia as the most prominent cord symptom, pyramidal and vesical symptoms, intracranial signs, lower motor neuron signs more widespread than at the apparent sensory level, with a partial block on spinal manometry and certain features of lipiodol study as emphasized by Moniz.

4. The characteristic pathologic features are lymphocytic infiltration and fibrous hyperplasia of the dura which may be adherent to the piaärachnoid, compression of the spinal roots and secondary degeneration of the cord, particularly of the posterior columns and the dorsal and ventral spinocerebellar tracts; chronic circulatory insufficiency with resultant myelomalacia of the gray and white matter over several segments above and below the level of greatest involvement.

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A STUDY OF THE QUICK METHOD FOR THE QUANTITATIVE DETERMINATION OF PROTHROMBIN WITH SUGGESTED MODIFICATIONS.*

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Recent communications by Quick, Stanley-Brown and Bancroft,[14] Warner, Brinkhous and Smith,[24a] and Dam and Glavind[5a] have described various methods for the quantitative determination of prothrombin. Although all of these methods employ unphysiological procedures and measure the amount of prothrombin indirectly, the data suggest that such a test has practical clinical importance. Subsequent studies have led these investigators[2,5b,13a] to conclude that the defect in the coagulation of the blood in certain cases of jaundice is due to a deficiency of prothrombin. Prothrombin estimations have been used to determine which cases of biliary tract disease possess a hemorrhagic diathesis and to study the efficacy of various therapeutic agents in the treatment of this condition. The newer

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methods have also been used to examine the relative amounts of prothrombin in hemorrhagic chick disease of dietary origin, in hemorrhagic disease of the newborn, in toxic sweet clover disease, in hepatic injury due to chloroform intoxication, in subjects with biliary fistula, and in other hemorrhagic diseases.

The present investigations were limited to a critical study of the Quick method for the quantitative determination of prothrombin. Quick and his co-workers[13a,b,14] and others[24b] state that the coagulation time of oxalated plasma, when mixed with an excess of thromboplastin and then recalcified, is a measure of the amount of prothrombin present. The importance of using an optimal amount of calcium for recalcification has been emphasized in a preliminary report.[21] The present observations present more data on the effect of calcium, suggest certain modifications and call attention to errors to be avoided in an effort to provide a simple and more accurate method of determining plasma prothrombin. Prothrombin values on a group of patients with liver and biliary tract disease are presented.

Methods. The present studies were limited to observations on human subjects. The methods followed were essentially the same as those described by Quick.[13a,c] The prothrombin time was determined on 0.1 cc. portions of oxalated plasma in clean, dry 100 by 13 mm. test tubes in a water bath at 37.5° C. A constant temperature was found to be essential. An excess of thromboplastin was supplied by the addition of 0.1 cc. of a freshly prepared saline suspension of tissue extract from rabbit brain. One-tenth cubic centimeter of an optimal calcium chloride solution was added with a blow pipette, and the time required for coagulation after the addition of calcium was observed with a stopwatch. It was noted that the end-point was always sharp and definite regardless of whether the time was normal or prolonged. Hereafter in this communication any determination of the prothrombin time includes the addition of an excess of thromboplastin in the above manner.

The thromboplastin was prepared from fresh rabbit brain by extraction with acetone U.S.P. as described by Quick.[13a] This preparation proved to be a satisfactory source of a potent tissue extract. It remained stable in a dry form at 5° C. for approximately 4 weeks. A more uniform preparation of the saline suspension of dehydrated material was obtained if it was incubated at 50° C. for 15 minutes, rather than at 45° C. for 10 minutes as Quick[13a] advised. Thromboplastin thus prepared failed to cause coagulation when mixed with fibrinogen and calcium.

Experimental. *Effect of Calcium Concentration.* Variable prothrombin times were obtained with normal plasma when the recalcification process was carried out with 0.1 cc. of the 0.025 M calcium chloride solution used by Quick.[13a,d] Usually it was impossible to obtain a fibrin clot in normal plasma in from 12 to 13 seconds unless the concentration of calcium was altered.

A stock solution of 0.1 M calcium chloride was prepared by dissolving 1.11 gm. of anhydrous chemically pure calcium chloride in 100 cc. of distilled water. Eleven solutions of calcium chloride, varying in concentration from 0.1 M to 0.000625 M, were prepared by diluting this stock solution. The effect of each of these solutions as a

recalcifying agent in determining the Quick prothrombin time was studied on the plasma obtained from 85 normal subjects.* The results obtained in each subject were similar. The observations on 1 typical case are shown in Table 1. The data obtained on a case of obstructive jaundice with a hemorrhagic diathesis are presented in this table for comparison. The findings clearly show that an excess of calcium as well as an insufficient amount of calcium prolonged the coagulation time. The optimal amount of calcium which was required to obtain a minimal coagulation time varied from individual to individual although usually recalcification with 0.1 cc. of a 0.01 M, 0.005 M or 0.0025 M calcium chloride solution was optimum. With optimal recalcification the normal prothrombin time was found to be 10 seconds. Not a single individual in the group of 85 normal persons studied showed a prothrombin time longer than 10 seconds. A coagulation time slightly shorter than 10 seconds was occasionally observed. Under these circumstances it appears reasonable to conclude that a 10-second prothrombin time may be considered to indicate the presence of 100% prothrombin.

TABLE 1.—EFFECT OF CALCIUM CONCENTRATION ON PROTHROMBIN TIME OF PLASMA FROM A NORMAL AND ABNORMAL SUBJECT.

Molar concentration of calcium chloride.	Coagulation time in seconds.	
	Normal.	Jaundice.
0.1	46	340
.05	22	73
.033	15½	49½
.025	14	40
.02	13	38
.015	12	32
.01	11	32
.005	10	29
.0025	10½	29
.00125	18	50
.000625	38½	124

The effect of calcium concentration was more critically studied on plasma obtained from 6 normal subjects in an effort to compare the optimal amount required for the determination of the prothrombin time with the total calcium of the blood serum. The amount of calcium present in the plasma after oxalation varied from 0.5 to 2.0 mg. per 100 cc. Most of the calcium oxalate was thrown down with the blood cells during centrifugation. The calcium chloride solution for this particular experiment was prepared by dissolving 2.5 gm. of reagent pure precipitated calcium carbonate in a slight excess of N hydrochloric acid. The slight excess acid was neutralized to pH 7.4 by the addition of 0.1 N sodium hydroxide and made up to 1000 cc. with distilled water. One cc. of this solution contained

* In all the prothrombin values presented in this communication this same technique for recalcification was followed.

1 mg. of calcium in the form of calcium chloride. A series of 21 calcium chloride solutions was prepared from this solution in such concentrations that when 0.1 cc. was mixed with 0.1 cc. of thromboplastin and 0.1 cc. of plasma, the calcium concentration varied from 3 to 17 mg. per 100 cc. When the calcium concentration was between 8 and 13 mg. per 100 cc., a normal 10 second prothrombin time was obtained on each of the 6 plasmas tested. The prothrombin times obtained when the calcium values were less than 8 and more than 13 mg. per 100 cc. were prolonged. Therefore, although the recalcification of plasma is an artificial process, the optimal amount of calcium required for coagulation *in vitro* was very similar to normal blood serum values for calcium.

Effect of Oxalate Concentration. The effect of oxalate concentration on the prothrombin time was studied on the plasma obtained from 6 normal individuals. Four and a half cubic centimeter samples of blood obtained by venipuncture were immediately mixed with 0.3, 0.4, 0.5, and 0.6 cc. respectively of a solution of 0.1 M sodium oxalate and centrifuged. The prothrombin time was determined in the usual manner on each of these plasmas. The results showed that the amount of calcium required to form a fibrin clot in 10 seconds varied slightly in proportion to the amount of oxalate present. However, since the optimal amount of calcium was determined in each instance, slight variations in the oxalate concentrations would not affect the prothrombin time. In all subsequent studies a 4.5 cc. sample of venous blood was oxalated with 0.5 cc. of 0.1 M sodium oxalate solution as described.[13a]

Simultaneous determinations of prothrombin were made on normal plasma which had been oxalated with equal amounts of 0.1 M sodium oxalate in the wet and in the dry forms. There was no essential difference in the results.

TABLE 2.—EFFECT OF LIPEMIA ON PROTHROMBIN TIME OF NORMAL PLASMA.

Molar concentration of calcium chloride.	Coagulation time in seconds.	
	Clear plasma.	Grossly lipemic plasma.
0.1	38	32
.05	17	15
.033	13	12½
.025	12½	10
.02	12	10½
.015	11	9
.01	11	9
.005	10	8½
.0025	10	8½
.00125	15½	9½
.000625	29	20

Effect of Lipemia. During the course of these observations it was noted that normal plasma possessing a gross lipemia frequently had a prothrombin time of less than 10 seconds. Prothrombin determina-

tions were made upon 3 individuals immediately after taking a low fat diet for a period of 24 hours. Each subject was then given a meal containing 120 gm. of fat and the prothrombin reading was repeated after 2 hours. The plasma obtained 2 hours after the high fat meal showed a gross lipemia. The results in one typical experiment are shown in Table 2. These data suggest that a markedly lipemic plasma has a shorter prothrombin time than clear plasma. The explanation of this phenomenon is not clear.

Relation Between the Prothrombin Time and the Concentration of Prothrombin. Since these studies indicated that with optimal recalcification the normal prothrombin time was 10 seconds rather than 12 to 13 seconds, it was necessary to reconstruct the graph permitting

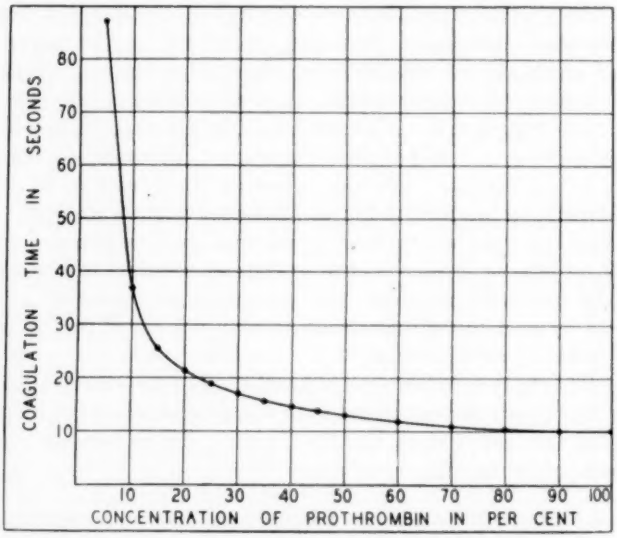

FIG. 1.—Relation of the prothrombin time, determined by the modified Quick method, to the concentration of prothrombin in human plasma.

the conversion of the prothrombin time to the percentage concentration of prothrombin. The data for the graph devised by Quick[13a] were obtained by determining the prothrombin time of various dilutions of normal plasma, with saline, or with other plasma rendered free of prothrombin by treatment with aluminum hydroxide.[13b,e,14] While repeating these studies with saline dilutions of plasma it was always noted that it was difficult to judge the time of clot formation in the dilutions containing 30% or less plasma because of the slow and scanty fibrin formation. Under these conditions a reduction in prothrombin was accompanied by a similar reduction in fibrinogen. This alteration of the amount of fibrinogen introduced an error into the determination of prothrombin since it did not

parallel the usual *in vivo* condition. For example, it is agreed that a significant alteration of fibrinogen does not exist in cases of obstructive jaundice with abnormal bleeding, but recent studies strongly indicate that a prothrombin deficiency is usually present.

Fibrinogen was prepared from normal human oxalated plasma as described by Eagle.[6a] The material prepared in this manner did not coagulate upon the addition of thromboplastin and calcium. Fibrinogen was dissolved in 0.85% sodium chloride solution so that the final concentration was 600 mg. per 100 cc. Various dilutions of a normal plasma were made with the saline solution of fibrinogen and the prothrombin time determined on each. The maintenance of a fairly constant fibrinogen content in the various plasma dilutions resulted in the formation of a normal fibrin clot with a sharp end-point regardless of the prothrombin time. The procedure was repeated with plasma obtained from 5 other normal young adults of both sexes with very similar results. The prothrombin time obtained with each dilution of plasma from each subject was averaged. Assuming that a 10-second coagulation time was normal and was equivalent to a 100% concentration of prothrombin, these composite figures were converted into graph form (Fig. 1). The graph coincided closely with that presented by Quick[13a] except that, in general, the prothrombin times were shorter.

Prothrombin Values in Individuals With Liver and Biliary Tract Disease. Abnormally low prothrombin levels have been observed in 23 patients in this clinic with various forms of liver or biliary tract disease. The data are presented in Table 3. A control prothrombin time was done on a normal plasma in every instance. Twenty-three patients with jaundice who had normal prothrombin values are not included. Additional data on the bleeding and blood coagulation times are presented in the table for comparison with the prothrombin estimations. The coagulation times of venous blood were determined by a method previously described[12] which gave normal values of from 6 to 12 minutes. Blood platelet counts and the clot retraction were normal in every case.

In this series, 7 patients showed a definite bleeding tendency. Cases 1, 9, 13, and 17 died as the result of hemorrhage. The bleeding tendency in these 7 individuals was associated with a marked decrease in the prothrombin level. The Ivy[9] bleeding time was prolonged in 5 of 6 of these cases with abnormal bleeding. The bleeding time by the Duke method was normal in every case. A few patients presented very low prothrombin values and yet escaped actual bleeding. The data are insufficient to establish the prothrombin level at which serious bleeding is to be anticipated. The intensity and duration of the jaundice showed no correlation with the decreased prothrombin values.

Discussion. Howell[8a] first described a method for measuring plasma prothrombin. This method consisted of noting the time

required for coagulation after the recalcification of plasma. Recently 3 more satisfactory methods for the quantitative determination of prothrombin have been described and applied to clinical investigations. The method described by Quick[13a] improved the Howell technique by adding an excess of tissue extract to insure the complete conversion of prothrombin to thrombin. Dam and Glavind[5a,b] revised the method described by Schønheyder,[18] and estimate prothrombin in terms of the amount of standardized tissue extract which it is necessary to add to a heparinized blood sample in order to cause coagulation in 3 minutes. Smith, Warner, and Brinkhous[19,24a] have developed an elaborate prothrombin method requiring 2 stages. The first stage is concerned with the conversion of

TABLE 3.—PROTHROMBIN VALUES IN INDIVIDUALS WITH LIVER OR BILIARY TRACT DISEASE.

Case.	Diagnosis.	Prothrombin, %.	Icterus index.	Coagulation time in minutes.	Bleeding time (Duke) in minutes.	Bleeding time (Ivy) in minutes.	Bleeding tendency.
1	Common duct stone†	35	20	7	3	3	Died postop. of intra-abd. hem.
2	Common duct stone*	72	90	12	1	5	None
3	Common duct stone*	60	25	8	½	4	None
4	Common duct stone (Ball valve)*	80	15	..	1	..	None
5	Common duct stone*	65	75	..	1	..	None
6	Adhesions about common bile duct*	30	80	12	1	6½	Subconjunctival hem. Gums bled
7	Adhesions about common bile duct*	72	45	8	2	3	None
8	Congenital absence of bile ducts*	15	50	..	2	..	None
9	Carcinoma of pancreas†	16	200	20	3	13	Died of subd. hemat.
10	Carcinoma of pancreas*	40	45	9	1½	6½	None
11	Cholelithiasis*	15	60	10	½	9½	Bled excessively from operative wound
12	Cholelithiasis*	65	2	..	1	..	None
13	Cholelithiasis†	15	12	..	2½	..	Died postop. of intra-abd. hem.
14	Chronic cholecystitis*	35	20	10	1	5	None
15	Liver abscess with biliary fistula*	28	75	13	1	21	Bled excessively from operative wound
16	Atrophic cirrhosis of liver	25	50	6½	2	4	None
17	Cirrhosis of liver†	9	75	12	½	5	Died postop. of intra-abd. hem.
18	Atrophic cirrhosis of liver	40	7	12	½	5	None
19	Atrophic cirrhosis of liver	50	20	10	1½	2	None
20	Atrophic cirrhosis of liver	47	35	12	1	5	None
21	Atrophic cirrhosis of liver	38	15	10	2	5	None
22	Atrophic cirrhosis of liver	50	18	8	1	3	None
23	Acute catarrhal jaundice	70	25	8	1	7	None

* Denotes operative diagnosis. † Denotes autopsy diagnosis.

prothrombin to thrombin in a sample of defibrinated plasma. Fibrinogen is then added to serial dilutions of the thrombin solution and the resulting coagulation times are considered to be an index of the prothrombin content of the parent plasma.

The Quick method for the quantitative determination of plasma prothrombin has the advantage of simplicity. Investigations[3a,b,c,13a,15] have demonstrated its value in the study of the hemorrhagic diathesis in certain cases of jaundice. The test has been criticized because the final reading includes the time required for the conversion of prothrombin to thrombin as well as the time required for the thrombin formed to react with fibrinogen. However, experiences suggest that if the test is limited to human plasma this variable is not of great importance.

It is well known that an excess of any neutral salt preserves the fluidity of the blood. Horne,[7] Sabbatani,[17] Rettger,[16] and Stassano and Daumas[20] observed the anticoagulant properties of large amounts of calcium. The present studies demonstrate that the presence of an excess of calcium as well as an insufficient amount of calcium prolongs the Quick prothrombin time. It was also observed that an excess of sodium chloride or bile salts in the test tube set-up caused prolongation of the prothrombin time. The optimal amount of calcium necessary to give the minimal coagulation time (prothrombin time) varied from individual to individual. The present observations indicate that if calcium chloride solutions of 0.01, 0.005, and 0.0025 M concentrations are used as recalcifying agents, in the determination of prothrombin by the Quick method, the minimal coagulation time will be obtained. Optimal recalcification gives a normal prothrombin time of 10 seconds. It is especially important that the recalcification be optimal when studying pathologic bloods. Although the recalcification of plasma is an artificial and unphysiologic process these data indicate that the optimal calcium concentration necessary for coagulation of oxalated plasma *in vitro* parallels normal blood serum values for calcium. It is suggested that a control prothrombin time on normal plasma should be done on each occasion to assure proper activity of the thromboplastin and the absence of calcium contamination of the glassware.

The nature, source, and mode of action of prothrombin are widely disputed. Prothrombin is known only by its capacity to form thrombin. Some investigators[4,8b,10,11] identify the source of prothrombin with the platelets as well as plasma; others,[1,6b] imply that it resides chiefly in the non-cellular plasma. Certain authors[22] deny the existence of a prothrombin factor in the coagulation mechanism. Recent evidence[19,23] indicates that the liver plays an essential rôle in the manufacture of prothrombin. Absolute proof that the newer methods for estimation of plasma prothrombin actually measure this substance is lacking. However, the present observations confirm those of others[3a,b,c,13a,15] in that the Quick prothrombin method measures a deficiency which frequently exists in certain

individuals with jaundice. Apparently this deficiency is responsible for the bleeding tendency in these cases.

The investigations on patients with low prothrombin values are being continued. The results, with special reference to various therapeutic efforts, will be reported in a future publication.

Conclusions. 1. The Quick method for the quantitative determination of plasma prothrombin contains variables which significantly influence the results of the test.

2. Calcium is an important variable in the Quick prothrombin method. The optimal amount of calcium necessary for recalcification must be determined in each instance to assure a minimal coagulation time (prothrombin time). Studies on the plasma of 85 normal individuals indicate that with optimal recalcification the normal prothrombin time is 10 seconds.

3. The optimal calcium concentration required for the determination of the Quick prothrombin time is similar to normal blood serum calcium values.

4. Slight variations in the oxalate concentration of the plasma do not influence prothrombin determinations if the optimal amount of calcium required is determined in each case.

5. The presence of a gross lipemia significantly shortens the prothrombin time. It is suggested that in order to avoid this variable determinations should be done only on clear plasma.

6. Observations on 46 individuals, with liver or biliary tract disease, indicate that the modified Quick prothrombin method measures a deficiency which frequently exists in these cases, and which is apparently responsible for the bleeding tendency.

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OBSERVATIONS ON HUMAN BLOOD STORED AT 4 TO 6 DEGREES CENTIGRADE.

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The blood bank idea has been received with considerable enthusiasm both in this country and abroad, and a number of "banks" are now in operation. Until recently, however, no adequate studies of the effect of preservation on the blood have appeared. These recent studies indicate that the enthusiasm for this innovation in transfusion methods is not entirely justified.

Observations on 10 samples of human blood kept at 4° to 6° C. over a period of 20 days are herein reported. The results appear in Table 1. These are in agreement with those of Kolmer[5] (in so far as they are parallel) and also with those of Rhoads and Panzer.[8]

Blood was received into 20% sodium citrate to make a final concentration of about 0.4%, although in some instances this was 0.6%. The pH of the citrate after sterilization was 8. Of necessity, the bloods were thoroughly shaken whenever samples were to be removed, a procedure believed to accelerate hemolysis. Hemolysis, however, was not obviously more marked in these specimens than in others remaining undisturbed in the refrigerator for an equal number of days, nor did red cell counts, which were made with each hemoglobin determination, show significant decreases. Fragility tests were done on cells that had been washed in 0.85% saline to remove traces of hemoglobin which had diffused on standing. Prothrombin by two methods was done on the citrated blood, and not on oxalated blood as required in the strict technique. Quick[7] regards Howell's prothrombin time as a measure of the thromboplastin rather than of prothrombin. Howell's method was used, therefore, with the idea of demonstrating in what manner disintegration of the platelets might affect the thromboplastin content of stored blood.

The most important changes observed in these samples of stored blood were an increase in the fragility of the red cells, disintegration of the granulocytes, and impairment of the properties of coagulation, all progressive. The fall in carbon dioxide combining power of the bloods and in blood sugar, although marked, are probably not important items in a transfusion medium. These changes, with the exception of Quick's prothrombin time, began at once and

individuals with jaundice. Apparently this deficiency is responsible for the bleeding tendency in these cases.

The investigations on patients with low prothrombin values are being continued. The results, with special reference to various therapeutic efforts, will be reported in a future publication.

Conclusions. 1. The Quick method for the quantitative determination of plasma prothrombin contains variables which significantly influence the results of the test.

2. Calcium is an important variable in the Quick prothrombin method. The optimal amount of calcium necessary for recalcification must be determined in each instance to assure a minimal coagulation time (prothrombin time). Studies on the plasma of 85 normal individuals indicate that with optimal recalcification the normal prothrombin time is 10 seconds.

3. The optimal calcium concentration required for the determination of the Quick prothrombin time is similar to normal blood serum calcium values.

4. Slight variations in the oxalate concentration of the plasma do not influence prothrombin determinations if the optimal amount of calcium required is determined in each case.

5. The presence of a gross lipemia significantly shortens the prothrombin time. It is suggested that in order to avoid this variable determinations should be done only on clear plasma.

6. Observations on 46 individuals, with liver or biliary tract disease, indicate that the modified Quick prothrombin method measures a deficiency which frequently exists in these cases, and which is apparently responsible for the bleeding tendency.

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OBSERVATIONS ON HUMAN BLOOD STORED AT 4 TO 6 DEGREES CENTIGRADE.

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The blood bank idea has been received with considerable enthusiasm both in this country and abroad, and a number of "banks" are now in operation. Until recently, however, no adequate studies of the effect of preservation on the blood have appeared. These recent studies indicate that the enthusiasm for this innovation in transfusion methods is not entirely justified.

Observations on 10 samples of human blood kept at 4° to 6° C. over a period of 20 days are herein reported. The results appear in Table 1. These are in agreement with those of Kolmer[5] (in so far as they are parallel) and also with those of Rhoads and Panzer.[8]

Blood was received into 20% sodium citrate to make a final concentration of about 0.4%, although in some instances this was 0.6%. The pH of the citrate after sterilization was 8. Of necessity, the bloods were thoroughly shaken whenever samples were to be removed, a procedure believed to accelerate hemolysis. Hemolysis, however, was not obviously more marked in these specimens than in others remaining undisturbed in the refrigerator for an equal number of days, nor did red cell counts, which were made with each hemoglobin determination, show significant decreases. Fragility tests were done on cells that had been washed in 0.85% saline to remove traces of hemoglobin which had diffused on standing. Prothrombin by two methods was done on the citrated blood, and not on oxalated blood as required in the strict technique. Quick[7] regards Howell's prothrombin time as a measure of the thromboplastin rather than of prothrombin. Howell's method was used, therefore, with the idea of demonstrating in what manner disintegration of the platelets might affect the thromboplastin content of stored blood.

The most important changes observed in these samples of stored blood were an increase in the fragility of the red cells, disintegration of the granulocytes, and impairment of the properties of coagulation, all progressive. The fall in carbon dioxide combining power of the bloods and in blood sugar, although marked, are probably not important items in a transfusion medium. These changes, with the exception of Quick's prothrombin time, began at once and

were well advanced by the fifth day. The alterations in all the bloods were similar in character and magnitude.

On the basis of these observations it is apparent that stored blood should not be used in the treatment of agranulocytic angina, if the expectation is to restore granulocytes. Whether the disintegration products of these cells could still serve as a stimulant to the manufacture of new granulocytes is, of course, a speculation. The same restriction, obviously, should apply to purpura hæmorrhagica and to hemophilia because of the diminution of platelets and their product, to vitamin K deficiency, and probably to all hemorrhagic diatheses. We have had no opportunity, however, of observing the effect of bank blood in these diseases under controlled conditions.

The significance of red cell fragility changes in stored blood is not so easily decided. If the belief of Yorke and Nauss,[9] of Baker and Dodds[1] and of DeGowin *et al.*,[3] that the harmful effects of hemolytic transfusion reactions result from the blocking of renal tubules by hemoglobin precipitated in acid urine, be accepted, blood should not be used after the first or second day of storage. On the other hand, this fragility is only accompanied by a trivial amount of lysis of erythrocytes during storage, probably attributable to the property of plasma to protect against hemolysis. It is important to note, too, that the oxygen capacity of these cells is not impaired. Moreover, the great majority of patients who receive such blood show no evidence of intravascular hemolysis. It appears that jaundice and hemoglobinuria are somewhat more frequent after infusion of stored blood than after fresh blood. Fox[4] reports an incidence of 14% for the former, 3% for the latter. Such occurrences are not, however, in most instances, accompanied by other evidences of true hemolytic reactions such as chills, fever and impairment of renal function, as might be expected. The hemoglobin in these cases passes out in the urine without any apparent harm, recalling the experiments of Bayliss.[2]

In 400 consecutive transfusions with stored blood, jaundice or hemoglobinuria of a harmless character, or both, were observed 7 times. They did not appear to be related closely to the age of these bloods, which averaged 10 days, for in 12 other transfusions with an average blood age of 16 days no evidence of hemolysis was observed. In addition, there were 3 classical hemolytic reactions, one of which was due to forwarding the wrong bottle of blood to the ward. Excluding this, our incidence of 2 true hemolytic reactions in 400 transfusions is not significantly greater than that for fresh blood as reported in medical literature. Other reactions occurred, characterized by chills and fever, urticaria, and so on, making an incidence of 10% in all, but these were not accompanied by evidence of hemolysis. A lower reaction rate for refrigerated than for fresh blood is reported from the Mayo Clinic.[6]

It is our opinion, by no means original, that true hemolytic trans-

fusion reactions represent something much more profound than simple intravascular hemolysis. Certainly hemolysis incidental to an acquired fragility of red cells should be distinguished from that of an antigen-antibody type of reaction. If this distinction be justified, then the incompatibilities causing true reactions are, in all probability, the same whether the blood be fresh, or stored; and consequently the danger of reaction with the two types of blood should be equal.

TABLE 1.—OBSERVATIONS ON 10 HUMAN BLOODS COLLECTED IN CITRATE AND STORED AT 4° TO 6° C.

Days	0	1	2	3	4	5	10	15	20
Hemoglobin	13.8	...	...	...	...	13.7	14.0	13.6	13.4
Oxygen capacity	18.8	19.3	18.1	19.4	18.5	18.5	18.5	18.6	18.0
Rbc. fragility (% NaCl)	0.44	0.48	0.49	0.60	0.60	0.68	0.75	0.83	0.85
Granulocytes (hundreds)	49	35	33	12	16	9	2	0.3	0.2
Prothrombin (Quick)	22	...	...	...	...	22	28	33	38
Prothrombin (Howell)	168	...	...	...	...	388	586	640	721
Platelets (thousands)	216	92	44	48	58	60	48	33	33
Isoagglutinin titer	57	...	...	...	...	57	57	44	27
Plasma CO_2	43	34	34	26	20	18	12	10	10
Glucose	97	72	55	43	43	33	13	10	?

Isoagglutinins were measured on 9 bloods, plasma CO_2 and glucose on 6. Figures are the average of observations for each day.

It would seem, from the results of this and other studies, that refrigerated blood should be used within a few days of collection, and that the arbitrary limit of 14 days allowed by some is much too long. Since a rapid turnover and prompt use is possible only in institutions performing large numbers of transfusions, 100 or more per month, a blood bank is apparently ill-advised for small hospitals.

Comparison of the therapeutic effects of stored and fresh blood in exact terms is not possible, but a canvass of the clinical staff of this hospital shows general satisfaction with the blood bank.

Summary. Important alterations in human blood stored in a refrigerator (a "blood bank") are recorded.

Such blood is clearly of less therapeutic value in some respects than fresh blood; but it is apparently of equal value in other respects. Its use is not accompanied by greater danger to the recipient than is that of fresh blood.

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THE COLLECTION AND PRESERVATION OF PLACENTAL BLOOD FOR TRANSFUSION PURPOSES.*

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Until the past few years, it always has been thought necessary to collect fresh blood at the time a transfusion was to be given. Recently this technique has changed considerably, and at present in many of the larger medical centers preserved blood has been used extensively. The first reports came from Russia,[1,11,14,17] where they definitely proved that this blood was usable and of value. There was a demand, however, for a source of supply which would be available in any general hospital. With this in mind they turned to the obstetric department and its potential reservoir of placental blood.[2,15]

Independently, on this continent, Goodall[9] and his associates at Montreal started the collection of placental blood while working on an experimental procedure aimed to test the result of the reduction of intraplacental tension on the third stage of labor. They have collected and preserved blood for 2 years and at last reports[8] they were satisfied with the use of the placental blood for transfusions. It was effective and they had had no untoward reactions. Recently Grodberg and Carey[10] have reported the use of this type of preserved blood at the Boston City Hospital.

We first studied the Montreal technique[9] and have directed our investigation along the following lines: 1. Development of the technique of collection and preservation; 2, the effect on the mother; 3, assurance of its safety for use; 4, proof of its value.

Collection and Preservation. We have set forth the following conditions which determine the cases suitable for collection of blood: *a*, The mother must be free from transmissible disease; *b*, the membranes must not be ruptured over 48 hours; *c*, there must not be obvious infection; *d*, the baby must be at or near term; *e*, the baby may not have asphyxia pallida; *f*, the presentation may not be breech or transverse.

* Read before the Syracuse Academy of Medicine, December 20, 1938.

Method. All mothers have antepartum Wassermann and flocculation tests of their blood. As an added precaution, blood is taken from the cord after delivery of the placenta for serologic examination.

The equipment we use is as follows: A 6 by 12 in. white enamel tray; a 500 cc. Erlenmeyer flask or Pyrex bottle; a Davol Sani-tab rubber cap; two 65 mm. test tubes; one 75 mm. Pyrex funnel with a special 80 mm. stem; one wood block 4 by 4 by 4 inches in which there are two holes to fit the small test tubes; one towel with a 3 by 3 inch hole, and one medicine glass. This is prepared as follows for collection of blood: The 500 cc. Erlenmeyer flask or Pyrex bottle will be stoppered by the rubber cap which provides an air tight seal and keeps the top of the flask sterile. This flask is placed on the tray lying on its side. In the two holes of the block are the small 65 mm. tubes, one empty and one containing 2 to 3 cc. of preserving fluid. The empty tube is for the collection of serum, and the tube containing the fluid is for a cell-suspension. Wrapped in a towel beside the flask and block is the Pyrex funnel. The towel with the hole in its center and the medicine glass complete the contents of the tray. This set is wrapped and autoclaved for 20 minutes at 15 pounds' pressure. When ready to be used the tray is simply unwrapped and placed on a table beside the sterile delivery table. The scrub nurse removes the contents of this tray to the delivery table, thus maintaining sterility.

The preserving fluid is made up so that each 1000 cc. contains 20 gm. of dextrose, 5 gm. sodium citrate (0.5%) and 4.6 gm. of sodium chloride. C.P. chemicals are used, and the final solution is isotonic. It is made as two solutions—one containing the dextrose, the other the salt and citrate, each in 500 cc. volume. These are then apportioned 50 cc. to a flask and sterilized; then one of each type poured into the collecting flask just before collection of the blood. This method entirely avoids caramelization of the sugar. However, the combined solution is used in the small test tube when the set is made up. Slight caramelization occurs but is not detrimental in preserving the cells for grouping and cross matching.

As soon as the baby is born the cord is clamped and cut. The baby is first attended, and, when its condition is satisfactory, it is placed in the crib. The blood is then collected. The end of the delivery table is partly lowered or in the case of the double table the two portions are separated. The physician who is to collect the blood strips back the last 2 inches of the cord, and, with his hand, holds it at the upper limit of the stripping. The stripped portion of the cord is cleansed with 70% alcohol and the end of the cord is cut off. The towel with the hole in its center is thrown over the operator's hand in such a fashion that the freshly cut tip of the cord and the hand extend through the hole. The towel is now in position to prevent any splashing from the vulva or the rectum from entering the funnel and flask. The assisting nurse has in the meantime placed the funnel into the mouth of the flask and at the proper time holds it beneath the tip of the cord. The blood is allowed to flow freely into the funnel. The operator is careful not to squeeze the cord during this early period of collection, because once the cord is compressed, the blood may stop flowing as coagulation occurs rapidly at the point of injury. During the entire collection the assistant gently agitates the flask with a rotary motion in order to prevent clotting of the blood before it is thoroughly mixed with the preserving fluid. When the flow of blood becomes slow, pressure is applied to the fundus of the uterus through the abdomen to force out the remaining blood. When this is accomplished, the cord is gently stripped until there is no more blood in the vessels. The last bit of blood is collected in the two 65 mm. tubes, 3 drops going into the tube containing the preserving fluid and approximately 1 cc. being collected in the other tube. A third tube is used to collect blood for the cord Wassermann test. The two small tubes are then placed in the

medicine glass. The funnel is removed, and the flask is sealed with the rubber cap. This keeps the top clean during subsequent handling. Once again the blood is thoroughly agitated with a rotary motion to insure complete mixing. The flask and each of the little tubes are labeled with the patient's name, date, and Wassermann reaction, and all are taken to the icebox. The flask is not opened again until the blood is used for a transfusion.

At a convenient time, preferably once every 24 or 48 hours, the new collections of blood are catalogued. The name and date on the flask and the two small test tubes are checked and recorded. The medicine glass containing the small test tubes is taken out of the icebox. The one containing clotted blood is centrifuged and the supernatant serum collected in capillary tubes which are sealed for storage. From the cell suspension in the second tube, the blood group is determined by means of known, potent group A and B sera. The sealed tubes of serum are now placed in the test tube containing the cells, this is labeled to correspond with the large flask, and then is stored according to group in a test tube rack in the icebox. A tag bearing the name, date, serology report and blood group is put on the flask of blood which is placed on the shelf used for blood of that group. A complete record is kept in a loose-leaf book, each blood being listed by its group classification, so that we can rapidly determine the number of flasks on hand in each group, their volumes, ages, and so on. Every flask of blood is kept in storage for 10 days, and then, if its appearance is normal, it is ready for use. By normal appearance is meant: first, that the rubber cap shows the presence of a slight vacuum, and second, that the supernatant plasma and preserving fluid is clear yellow with, at most, a just visible tinge of hemolysis immediately above the layer of settled red cells (the appearance may be slightly cloudy due to incomplete settling of the buffy layer present in citrated blood) If either or both are not present, the collection is discarded as possibly contaminated.

The icebox, which we have used for storage, is equipped with a constant temperature control which maintains 34 to 35° F. This was thought advisable for experimental work. Time has proved that a refrigerator equipped with a condensing unit of greater than standard capacity and a fan to circulate the air in the box will maintain a sufficiently constant temperature for preservation of this blood. It is suggested, where the refrigerator is to be sufficiently large, that the cooling unit be of the air-conditioned type. We say this because the one difficulty with the icebox described above is the problem of defrosting. If the standard refrigerator is used, the defrosting has to be carried on as rapidly as possible in order that the blood does not lose its chill.

Cross-matching and Transfusion. In using the blood for a transfusion, the blood group of the recipient is first determined, and then complete cross-matching is carried out with each of the desired number of flasks containing blood of the same group. This is done with the small tubes of cells and serum, and this method permits of several such tests for compatibility without touching the flask of preserved blood. One-half hour is the minimum time that the cross-matchings must stand before compatibility is passed on, but we prefer to wait 45 to 60 minutes because the reaction time of fetal blood is felt by some men to be slower than that of adult blood. We have not found this to be true so far. In grouping the recipient however, the reaction is usually apparent within 10 minutes and cross-matching can be started almost at once in urgent cases. When this is done, a final reading of the patient's group is always made again at the end of the half hour. In cross-matching and grouping we use the vaseline sealed hanging drop preparation in which drying of the suspension of cells and serum as well as contact with foreign substances or other trauma is eliminated.

The flasks of blood found to be compatible are now removed from the icebox, rotated gently to obtain an even suspension, and then are ready for use. It is not necessary to warm the blood before using it, for it will be nearly at room temperature when it enters the patient's vein. In fact, heating preserved blood may be a factor in producing reactions. Knowing a patient's group, we can at once pick out the needed number of flasks of the same group, and can be almost certain they will prove to be compatible on cross-matching. When the flask is used, the recipient's name and the date of use complete the record. In cases where time is not a factor, we have adopted the routine of giving the recipients enough sodium bicarbonate by mouth or sixth molar sodium r. lactate by vein to make the urine reaction alkaline prior to transfusing them, inasmuch as this has been shown to very probably eliminate the danger of anuria by a plugging of the kidney tubules with precipitated free hemoglobin if a reaction producing hemolysis should occur.[5,13] In emergency cases we make every effort to carry this out.

When the blood is nearly ready an intravenous infusion of isotonic saline is started on the patient, using an open burette of the familiar arsphenamine type as the container. The prepared blood is poured into the burette through a funnel, the top of which is covered by 6 thicknesses of washed sterile gauze, and allowed to run in by gravity. The funnel has been prepared previously and autoclaved with the transfusion set, and, just before using, it is washed by pouring sterile saline through it in order to remove any remaining bits of loose gauze. It is more or less characteristic of preserved blood to have a few small soft clots present in the flask. This may be due to the action of small amounts of Wharton's jelly. These are strained out by the gauze. The second flask of blood is poured into the burette when the first has almost completely run in, and the two may be separated by a small amount of saline solution, although this has not been found to be necessary. It is our practice to wash the last of the blood into the patient's vein with addition of some saline. The speed at which the blood is allowed to flow should be slow at first (3 to 5 cc. per minute) but may be increased as the transfusion continues to 10 to 15 cc. per minute. The average transfusion of 500 to 600 cc. will take about an hour to run in.

Experimental Data. Before using any of this blood for transfusions, it was felt that its value and safety should be established. We found, using the Russian preservative, which consisted essentially of 0.5% sodium citrate and enough sodium chloride so that the final solution was isotonic,* that hemolysis was apparent after 3 days of storage and had become marked at the end of 10 days. In spite of the successful 2-year transfusion record of the Montreal workers, we were hesitant about using blood apparently containing considerable free hemoglobin. It was suggested to us[7] that we experiment with the effect of sugar in the preservation of placental blood, inasmuch as the appearance of hemolysis had been found to be nearly coincidental with a sharp drop in the sugar content of preserved adult blood and could be largely prevented by the addition of glucose. It is interesting to note that, although Belenkiy[1] mentioned in 1936 that the addition of dextrose gave better preservation of blood, this method apparently has not been used until recently.[4,7] As shown in Figure 1, blood sugar observations on

* We used Citro-Seroid, during the early part of our work, made by Ayerst, Harris, and McKenna.

placental bloods quickly demonstrated that hemolysis appeared at the same time as a sudden fall in the sugar concentration from the previous level of 20 to 40 mg. % to zero. We then ran 3 series of flasks varying the original preserving fluid by adding dextrose in amounts of 2, 3, and 4 gm. respectively, thereby making the final solution hypertonic. A second group of 4 series of flasks was done adding the dextrose as an isotonic solution so that the actual amount of sugar present per flask was 0.5, 1.15, 2.5, and 3.75 gm. respectively, thereby keeping the final solution isotonic. Blood sugars were done in each group over a period of 90 days, at first daily, later 2 or 3 times a week, and finally once a week. The sugar values corresponded within reasonable limits of error to the amount of sugar

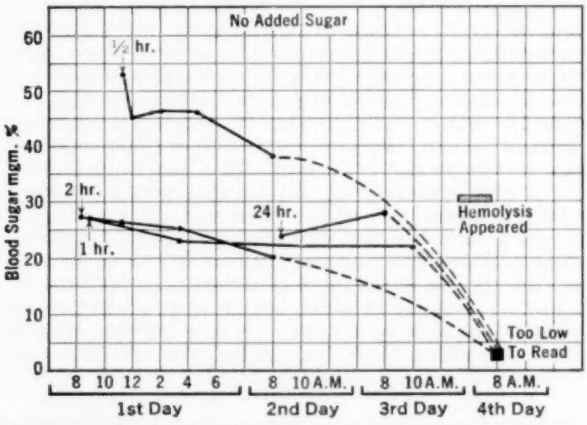

FIG. 1.—Blood sugar levels when isotonic saline and citrate (0.5%) was used as preservative. Note sudden disappearance of sugar on the fourth day.

added in each case. For instance, with 0.5 gm. of dextrose there was an average value of 240 mg. % and with 2 gm. a value of 900 to 1100 mg. %. The amount of preservative used was kept at 100 cc. per flask and the average amount of blood added was 85 cc.

It was found that there was a slow but steady drop in the sugar concentration during the period of storage with each of the series of flasks containing less than 2 gm. of dextrose. At the end of 80 to 90 days those containing 0.5 gm. of dextrose had fallen to zero, those with 1.15 gm. from 600 to 200 mg. %, but those with 2 gm. remained very nearly the same, falling only to 800 to 900 mg. % It was only in those flasks containing 2 gm. or more of added dextrose that the maximum delay in the development of hemolysis appeared. In this group, while hemolysis became evident almost as soon as in the absence of added sugar, it progressed very slowly and did not become marked until after 8 weeks of storage. Therefore, we have used 2 gm. of dextrose per flask, because this allows as much sodium

chloride as is possible in the preserving mixture with a concentration of sugar which will give the most satisfactory preservation. Since agitation of the blood increases the speed of hemolysis and probably actually produces a greater degree, the hemolysis in these flasks was affected because frequent mixing was necessary for the blood sugars. For the same reason, we cannot compare accurately the effect of the hypertonic and isotonic solutions. This has been demonstrated by a third series using the isotonic preservative in which the flasks have not been shaken up or disturbed except for observation of the degree of hemolysis (Fig. 2). This has shown a very slow development of hemolysis, being of slight degree at the end of 1 month, moderate at the end of 2, and marked only as the blood approached 3 months of storage.

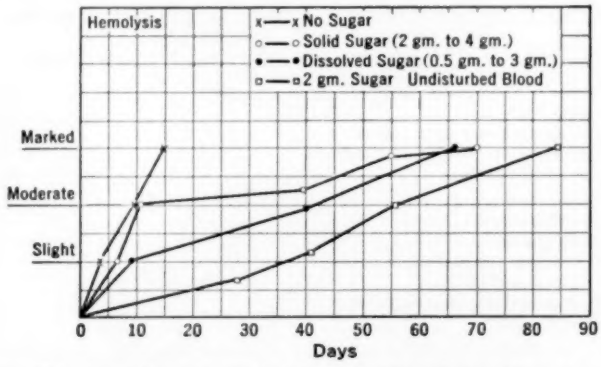

FIG. 2.—This shows the rate of development of hemolysis with various types of preserving fluid. The lowest curve, that of the undisturbed blood, shows the true effect of the addition of sugar. In the two middle curves the specimens were thoroughly mixed for the frequent sugar determinations.

In regard to the actual condition of the blood cells during the 3 months period of storage, successive stained smears at about 2-week intervals have shown that both the red and white cells remain quite normal in appearance (Fig. 3). We have also found that while the number of nucleated red cells tended to decrease, at least during the first 10 days, some of them were still present in the smear after 3 months.

A study of the red cell count and hemoglobin content was done on 67 unselected specimens as diluted by the preserving fluid (Fig. 4). The average red cell count was 2,023,000 (highest, 3,260,000; lowest, 920,000). The average hemoglobin (Haden-Hauser) was 7.4 gm. (3.75 to 11.3 gm.). The average total volume of 58 specimens was found to be 184 cc. with a range of 110 to 270 cc. In explanation of the lower volumes, it should be said that at times, before our collection technique was perfected, there was spilling of some of the 100 cc. of preserving fluid, originally placed in the collecting flask

before autoclaving, as well as poor collections of blood. The wide discrepancies that occurred in the relation of the red cell value to the volume can be accounted for partly by the above and partly by the variation known to exist in fetal blood values. Our figures for average values show that the diluted preserved placental blood is approximately equal to one-half the volume of average adult blood, but this ratio is not entirely reliable in estimating the amount of preserved blood needed for a given transfusion.

The initial experimental work was carried out with no pretense of sterility in handling the flasks of blood, in fact we did not even use sterile pipettes to withdraw the samples of blood. This was done because we did not then care whether or not these flasks remained sterile. We were curious to see how easily they might be contaminated. A total of 69 flasks were cultured from 1 to 4 times and 11 of these (Table 1) showed bacterial growth. In 8 instances the organ-

TABLE 1.—BACTERIOLOGY DURING EXPERIMENTAL PROCEDURES.

Number of specimens cultured	69
Begun in broth	71
Begun on blood agar plates	10
Begun by incubation of specimen	42
Total cultures made	123
Number showing growth	11
Bacillus subtilis	4
Staphylococcus albus	1
Hemolytic *Staphylococcus aureus*	1
Diphtheroid bacillus	1
Non-hemolytic streptococcus*	2
*Bacillus coli**	2

* The *B. coli* and one of the streptococci were obtained in the only 3 instances of collection in a breech delivery.

isms were thought to be laboratory contaminants; in the remaining 3 which were breech deliveries, *B. coli* was found in 2 and the other may have been contaminated either at the time of collection or subsequently in the laboratory. With the exception of *B. coli*, the organisms listed in the table are common laboratory contaminants. In 4 other instances in which bacterial growth was found subsequent cultures were sterile.

Recently, we have begun culturing previously unopened flasks of blood after periods of storage varying from 6 to 90 days. At present, we have a total of 55 consecutive specimens all of which have been sterile (Table 2). These were cultured by incubation of 50 to 60 cc. of the preserved blood which was then plated on blood agar.

TABLE 2.—BACTERIOLOGY OF PREVIOUSLY UNOPENED SPECIMENS.

Number of consecutive collections cultured	55
Number showing bacterial growth	None

The collection of the blood involved only the third stage of labor. It was, therefore, necessary to prove that the mother was not harmed. We took two series of 86 cases each and compared the elapsed time of this stage of labor. In each series the mechanism was conducted

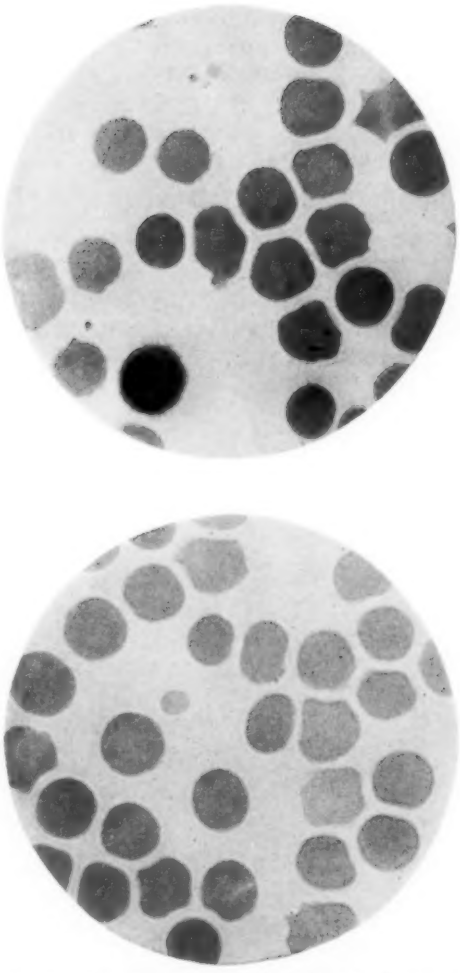

FIG. 3.—Two fields in a stained smear made from a flask containing blood which had been stored for 3 months. Note the nucleated red cell and the normal, well preserved appearance of the cells. (× 1200.)

in the same manner. The cases where the cord and placenta were emptied of their blood took 8 minutes $5\frac{2}{3}$ seconds for completion of the third stage. The cases where the cord and placenta were allowed to remain intact required 8 minutes and 5 seconds.

Comment. We feel that our present technique of collecting and storage is a safe, satisfactory, and efficient method of obtaining blood for transfusions.

We have shown that the labor mechanism of the patient from whom the blood is collected is not affected. Therefore, the procedure is not harmful to her.

While the cord Wassermann test has been shown to be unreliable as an absolute diagnostic criterion of congenital syphilis,[3,12,13] and therefore not done by some authors,[10] we add it to our precautionary measures as a further safeguard. The same fault can be found with

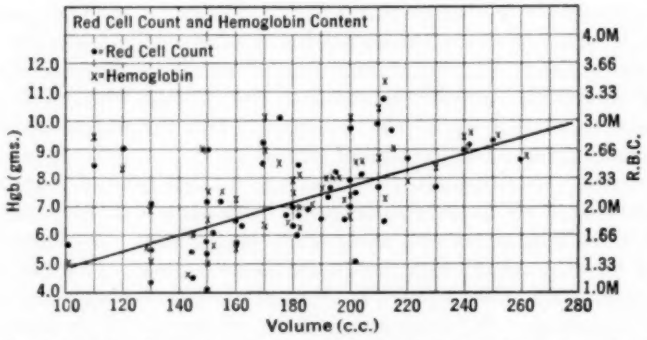

FIG. 4.—The red cell count and hemoglobin content of each specimen is plotted according to the volume. They tend to increase directly with the volume as indicated by the solid line representing the mean values.

most if not all of our serologic tests in adults. The literature contains many reports of false positive as well as false negative results during pregnancy. As long as the blood tests for the presence of syphilis are not absolutely reliable, we feel it is wise to take all reasonable care to exclude the possibility of transmitting this disease.

Further experimentation is being carried out with the preserving fluid, regarding its physical and chemical properties and the amount necessary to use. The addition of saline and glucose to the blood in the quantities used, gives a reasonably satisfactory preserving effect and, in most if not in all instances, this would add to the beneficial effect of the blood and certainly would not be harmful to the patient.

Several of the Russian workers[2,14,15,17] have used a citrate solution, as in the ordinary citrate transfusion, as the preservative. It is also used in this country as mentioned in the reports of Fantus and Scheimer,[6] and Grodberg and Carey.[10] Goodall[9] has used citro-seroid in his work. We began a year ago with citro-seroid but, as we have shown, obtained much better results with the addition of

dextrose. Karavanov[11] and Belenkiy[1], as far as we know, were the first to use the saline-citrate and dextrose-citrate preserving mixtures. DeGowin *et al.*[4] have just reported that preservation of adult blood is much more satisfactory with the addition of dextrose and feel that anaerobic storage will further improve preservation.

While we feel that our technique satisfactorily insures sterile preserved blood, the possibility of contamination with a pathogenic organism at the time of collection is, of course, always present. However, this is just as true in any other method of collecting blood for transfusion. If contamination should occur in the case of this preserved blood, one of two things would be true after the required 10-day period of storage. Either the organism would be so attenuated as to be non-pathogenic, or the change in the condition and appearance of the blood at this time, as previously stated, would at once indicate the presence of bacterial growth. We have not had the opportunity to observe this in our present series of cultures except for the collections from breech deliveries. Syphilis and other contagious diseases, significant abnormal findings in the mother, and blood dyscrasias or other diseases in the infants, are ruled out in the obstetric work-up of the cases used and the follow-up of the baby during the 10-day period of storage.

For most transfusions it is necessary to use two or more flasks of blood, and, we have in some cases, cross-matched the flasks used against each other as well as against the patient. We have never found any incompatibilities between flasks containing bloods of the same group, and have not felt it necessary to continue this additional cross-matching. We have given 18 transfusions to date without a severe or serious reaction. We did have in one of our first transfusions a mild reaction, consisting of a short chill and fever of 100°. This appeared an hour after the transfusion was finished and was not accompanied by urinary findings or other evidence of incompatibility of the blood. This transfusion was given quite rapidly and it may be considered a so-called "speed reaction"[5] or possibly due to pyrogen contamination. Both the Russian and American workers, using simple citrated blood,[2,6,14,15,17] have almost universally found that 10 to 12 days is the maximum period that the blood can be preserved in good condition. The Boston workers,[10] however, report a maximum of 30 days storage before use. It has long been felt that citrated blood could not be preserved more than a few days, at most, without the probability of deterioration of a degree sufficient to affect its safety and value for transfusions. Most of the reports of preserved citrated blood give a high percentage of reactions, some as high as 67%.[11] We have not enough data at present to verify our impression that these may be due to this method of preservation. However, Goodall[8] has had 2 years' experience using citro-seroid for preservation and has not had reactions following transfusions. We feel that the type of preservative may

be responsible for this record. Our method maintains the blood in a more perfect state of preservation and permits a longer period of storage than citro-seroid. The blood we have used for transfusing patients has been stored for periods of 10 to 50 days, and most of it has been between 20 and 35 days old.

Table 3 shows the data concerning the transfusions we have given. We realize that the number is too small to justify any definite conclusions concerning the value of this blood as compared to that of fresh blood. However, these observations support our contention that the preserved blood is approximately as effective as fresh adult blood for transfusion purposes. In every case we have noticed the clinical improvement which one expects to see following the average successful transfusion. The patients have been oberved carefully for any evidence of reaction to the preserved blood and but one instance has occurred, as previously mentioned. In no case has the urine shown any evidence of hematuria, nor has there been any clinical jaundice except in the case with hemolytic anemia, where it was present prior to the transfusion. The red count and hemoglobin have shown a fairly satisfactory increase in most instances. In transfusions 1, 11, 14, 15, 16, and 17 (3 cases) the presence of either dehydration, severe infection, or an active hemolytic process was perhaps responsible for the failure of the red cell values to rise. In 3 cases (4, 12, and 13) we did not obtain satisfactory counts for comparison. Our results with these 18 transfusions, we believe, show that the preserved red blood cells can be maintained for a period of at least 50 days, and probably longer, in a condition which permits them to again take up their original function in the blood stream. This has been evidenced in our series by the gain in the red count and hemoglobin values over a period of 12 days after transfusion. At the end of this time, the patients had either been given another transfusion or discharged from the hospital making a longer follow-up impossible. We have found no evidence that these preserved cells tend to disappear rapidly from the recipient's circulation, nor that the use of this blood is in any way detrimental to the recipient. However, the contention that it is just as good as fresh blood is not tenable for there are well known facts, such as the rapid disappearance of complement and loss of the property of coagulation which at once refute it.

The amount of preserved blood used at one time has varied from 125 cc. in a child to 1000 cc. in an adult who had a severe hemolytic anemia. Five to six hundred cc. is the average amount used, and, in our short experience, seems to be the approximate equivalent in effectiveness of the average transfusion of 400 to 500 cc. of undiluted citrated adult blood. This blood has been used in the treatment of shock, hemorrhage, infection, and anemia with good results. One of the most important features of the preserved blood is that it is always on hand in an emergency, and it is possible to have the

TABLE 3.—TRANSFUSIONS GIVEN WITH PRESERVED BLOOD.

Transfusions.	Diagnosis.	Before transfusion.			Transfusion.		Flasks used.		After transfusion.			Remarks.
		Date.	R.B.C. (mill. per c.mm.).	Hgb.* (%).	Amt. of blood given (cc.).	Date.	No.	Age in days.	Date.	R.B.C. (mill. per c.mm.).	Hgb.* (%).	
1	Prolonged labor with shock and dehydration	9/14	3.7	75	325	9/14	2	14 21	9/15	3.2	68	Rapid relief of shock.
2	Abruptio placentæ with hemorrhage and shock	9/22	3.1	45	595	9/22	3	17 18 30	9/29	3.3	49	Rapid relief of shock.
3	Placenta previa marginalis with hemorrhage and shock	10/15	2.2	45	475	10/15	3	20 21 21	10/24	3.6	55	Rapid relief of shock.
4	Postpartum bleeding with shock	..	..	..	475	10/9	3	26 31 33	10/10	3.3	52	Rapid relief of shock. (? of speed reaction.)
5	Premature delivery; acute pyelitis; anemia	10/14	2.2	23	355	10/16	3	23 26 30	10/18	2.3	26	Steady rise in r.b.c. and hgb. Infection subsided after delivery.
6		10/22	2.6	31	480	10/23	3	29 30 30	10/24	3.0	42	
7		10/25	3.5	45	455	10/27	3	26 29 34	10/28	4.1	49	
8	Ovarian cyst; chronic pelvic inflammatory disease; postoperative anemia	11/25	2.8	62	360	11/26	3	10 31 44	11/28 12/2	3.8 3.9	71 78	Good response.

9	Chronic lung abscess; anemia	11/18	3.8	58	620	11/19	3	10 20 24	11/20 11/23	3.7 4.1	65 65	Fair response.
10	Postoperative anemia and wound infection	11/28	3.3	65	600	11/29	3	10 27 50	11/30 12/1	3.7 4.1	75 81	Good response.
11	Acute hemolytic anemia (sulphanilamide)	1/2 1/4 1/5	5.0 2.5 1.8	.. .. (50)?	1000	1/5	6	21 21 23 24 26 27	1/6	1.8	..	No apparent response. However, after 500 cc. fresh blood on 1/6, r.b.c. was 1.3 mill., showing continued blood destruction.
12	Ruptured ectopic pregnancy with shock (about 1 pint of blood in abdomen)	2/12	(4.0)?	55	505	2/12	3	22 30 49	2/13	4.0	80	Good response. Relief of shock.
13	Postoperative shock	..	..	..	375	1/30	2	39 46	..	..	..	Rapid relief of shock.
14	Ruptured appendix; general peritonitis, empyema and pneumonia	2/17	4.0	85	225	2/18	1	30	2/20	4.0	68	Patient critically ill. Good clinical response. 500 cc. fresh blood given 2/28 with only a transient effect.
15		2/20	4.0	68	160	2/21	1	56	2/22	3.5	58	
16		2/22	3.5	58	190	2/22	1	31	..	..	..	
17		..	..	..	175	2/25	1	36	2/26 2/28	2.0 2.2	39 42	
18	Puerperal sepsis; pelvic abscess; B. hem. strep. infection with chills and fever	2/22	3.1	52	465	2/22	3	15 15 11	2/25	3.5	62	Good result.

There was no hematuric jaundice or unfavorable reaction except that Case 4 had a chill, 15 min., rectal temperature 101° F., and Case 11 had a marked gross hematuria from the day before to 2 days after transfusion and a deep red colored serum.

* Haden-Hauser, rarely Tallqvist.

transfusion in progress within less than 1 hour after being notified that blood is wanted.

Conclusions. 1. Following the procedures as described by us, any obstetric department may collect placental blood without interference with its normal routine or technique.

2. The blood may be collected without harm to the mother.

3. An isotonic solution of 0.5% sodium citrate, 4.6 gm. sodium chloride, and 2 gm. of dextrose per 100 cc. will satisfactorily preserve the blood for a period of 8 to 10 weeks in a condition suitable for transfusion use.

4. This method will provide an important source of blood which can be made constantly available for transfusion purposes.

5. We foresee an especial value in emergency transfusions because it takes less than 1 hour to group, cross-match, prepare the blood, and begin the transfusion under all reasonable circumstances.

6. The preserved placental blood is without danger from bacterial infection including syphilis, and it conforms to the New York State requirements for blood donors.

7. It is a safe and efficient form of blood for use in transfusing patients.

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BLOOD STUDIES ON THE NEWBORN.

I. Determination of Hemoglobin, Volume of Packed Red Cells, Reticulocytes, and Fragility of the Erythrocytes Over a Nine-Day Period.

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For more than 100 years blood studies on the newborn have furnished an interesting and at the same time contradictory chap-

ter in hematology. It has been widely accepted that increased values for hemoglobin, erythrocytes, volume of packed red cells, bilirubin and so on, are to be encountered in the blood of newborn infants,[25b,32,58b] although there are many reported instances where these high levels have not been substantiated. Investigations on the fragility of the red cells have led to considerable confusion, so that no definite picture of the situation has ever been accepted. It was this unsettled state of knowledge concerning fragility which led us to undertake the present study. We approached the problem, not so much to prove or disprove previous contributions, but rather to find what could be uncovered in the light of present-day methods, with special reference to the Evelyn photoelectric colorimeter[9,10] and the hemolytic index.[54] We shall confine ourselves in this paper to studies of the hemoglobin, volume of packed red cells and fragility of the red blood corpuscles, with brief notes on the reticulocytes; and later take up our findings in regard to the direct and indirect blood bilirubin in the infant, with discussion of icterus neonatorum and of several cases of erythroblastosis.

Without reviewing the literature completely, we find it desirable to include under the appropriate headings some of the more outstanding and contributory works of the past and present. It is interesting to note that as early as 1831, according to Bayer,[4] Denis first published figures on the blood of newborns. Later, in 1866, Kruger[29] observed that at birth the amount of hemoglobin in the blood of a newborn infant was equal to that of the mother, only to rise to a higher figure later. Then in 1878 Leichtenstern[31] pointed out that age and sex of the infant should be taken into consideration before drawing conclusions as to the normal levels, but others since have shown the differences to be negligible in the first few days of life. Schiff[45] in 1892 demonstrated that differences in values may be due to environment and geographic location. The exhaustive study of Williamson[57] in 1916 reported some of the highest hemoglobin values on record, probably due to the spectrophotometric method employed. This made a historic contribution to hematology and pediatrics. His work, using 16.9 gm. hemoglobin equivalent to 100%, is the only standardized investigation prior to 1924. Unfortunately, the early workers and many of the later ones, failed to state on what basis their values were made, so that a complete comparison is difficult, if not impossible. For example, some investigators, using the Haldane and Van Slyke methods, employed 13.8 gm. hemoglobin per 100 cc. blood as equivalent to 100%, while others used 17.2 gm., and so on. Others merely reported in terms of percentage. While it is true, as Guest and Brown[16] pointed out, that expression in percentage of normal standard means little when taken alone, we do feel, as did Haden and Neff,[19] that for the sake of comparison results should be expressed in percentages of a standard as well as in grams per 100 cc. Many workers have not given the dispersion of values from minimum to maximum, but have

been content to state the average figure for a series. This confuses the picture considerably and we feel this should be kept in mind when comparing results.

We shall not enter into a detailed discussion of the physiology of the newborn, into the anemias, diseases or theoretical problems of the infant, but will merely present our material as we found it in Montreal, offering such conclusions as we feel are justifiable.

Material. Normal, full-term white infants born on the wards of the Montreal Maternity unit of the Royal Victoria Hospital were taken for study, excluding from the series only those in whom serious illness or complications developed or on whom determinations were too incomplete to be of value. Several cases of erythroblastosis were taken as they occurred but are not included in the general findings. These will be taken up separately. We limited our study and survey of the newborns to a 9-day period, making determinations on the first (day of birth), second, fourth, sixth and ninth days. No attempt is anticipated to follow these infants later in the out-patient department. In all, we examined 65 newborns during the period of study, obtaining 5 complete studies on 29, 4 out of 5 on 12, and 3 or less on the remainder, with 5 of these disqualified due to illness or transfer. The newborns in the series were observed closely on the wards in order to detect the occurrence of icterus neonatorum, erythroblastosis, complications, and so on. The blood on the first day was obtained immediately from the umbilical cord, usually after cessation of pulsations at the time of delivery, placed in especially prepared vials containing 10 mg. of potassium (4 mg.) and ammonium (6 mg.) oxalate per 5 cc. blood, and sent directly to the laboratory. The bloods thereafter were obtained from the sagittal sinus by fontanel puncture, under the personal supervision of one of us, so that a constant quantity was obtained in the same manner and sent to the laboratory in the special vials. Determinations were made at once, or within a few hours of the time of withdrawal, for it has been known for some time that cord blood may readily hemolyze in oxalate or citrate solutions.[15,40]

Technique. Throughout this study, with the exception of the determinations of volume of packed red cells and reticulocytes, the Evelyn photoelectric colorimeter[9,10] was used. The colorimeter is a stabilized, direct-reading, single-photocell, photoelectric colorimeter which is equipped with light filters. Extensive and exhaustive usage and testing of the machine by Evelyn and coworkers have proved the value and accuracy of the apparatus, and we are indebted to him for his instructions and helpful suggestions. We employ this machine regularly for routine hemograms in the Pathological Institute, so that we feel we have a great familiarity with it. The colorimeter is also regularly employed in the laboratories of the Royal Victoria Hospital, the McGill University Clinic, and in other medical centers of the East.

For the hemoglobin determinations, a calibrated 0.05-cc. pipette was used to measure the blood, which was in turn added to 25 cc. distilled water in a standard colorimeter tube. A drop of concentrated ammonia water was added to insure complete and immediate hemolysis and the tube was placed in the machine and the hemoglobin read directly, using the filter which has a maximum transmission of 540 millimicrons. It has been previously found by one of us (Waugh) that a blood in which there are 5 million erythrocytes of normal size (95 cu. μ) and containing a normal amount of hemoglobin (hemoglobin concentration of 1) has 15.6 gm. of hemoglobin per 100 cc. of blood. This figure was determined by the Van Slyke method for oxygen capacity. This value is taken as 100%, and,

as may be readily seen, is preferable as a standard to any figure based upon simple estimations of total hemoglobin in normal individuals, which is subject to great geographic influences and other variables. We shall employ this value as our standard and as a base line for determining the differences seen in the blood of newborn infants. Foster and Johnson,[11] Haden[18] and Osgood[40] also found 15.6 to 15.8 gm. per 100 cc. to be standard (equivalent to 100%) for adults in their respective areas.

The regulation Wintrobe hematocrit tube[58d] filled with 1 cc. of whole blood was used for determining the volume of packed red cells. The determinations were made in duplicate and centrifuged for ½ hour at 3000 r.p.m. in a Type C International centrifuge. These results are expressed in percentage. We have found, using the anticoagulant which we employ, that the blood of an adult in which there are 5 million erythrocytes of normal size has a volume of packed red cells of 47.5% (Wintrobe[58d]). This value we take as our standard for comparisons. The reticulocytes were counted by the approved method, using the vital staining technique with brilliant cresyl blue, and counting the number of young forms per 1000 red cells. These counts were not made on all cases but on a sufficient number to be of some significance.

The fragility of the erythrocytes was determined by the methods developed first by Waugh and Chase[55] and later modified by Waugh and Asherman.[54] These methods provide for the use of Simmel's solution rather than isotonic sodium chloride, and now utilize the Evelyn colorimeter so that the degree of hemolysis can be calculated directly from the amount of hemoglobin liberated rather than by the tedious and variable procedures with enumeration of the red cells heretofore used. The reader is referred to the above papers for the preparation of the solutions and detailed technique. The pH of the solutions was carefully maintained at 7.1, as recommended by the authors, and was diluted and distributed into liter bottles labelled 100, 70, 65, 60, 55, 45, 40, 35, 30, indicating the percentage of the original solution. The blood was withdrawn and measured with a calibrated 0.02-cc. pipette and added to 10 cc. of each of the solutions in a standard colorimeter tube. The contents were mixed gently, the tubes centrifuged for 10 minutes at a low rate, then placed in the colorimeter and the amount of hemoglobin liberated read directly. From these readings the percentage of hemolysis (proportion of hemoglobin liberated to total hemoglobin) and an index of hemolysis, which is the sum of the percentages of hemolysis of all the tubes, are used to express the resistance of the cells to the solutions. Waugh and Asherman have found in examining the blood of healthy adults that the average index of hemolysis is 400, with a maximum normal resistance of 350 and a minimum of 450. It has been found that in obstructive jaundice of long duration the index falls to approximately 250, while in hemolytic jaundice it rises to the neighborhood of 650. The use of this index is advocated "as it offers a much readier and more precise means of expressing and recording the fragility of the red blood cells."

Hemoglobin. *Literature.* We shall not outline the literature prior to 1920, but shall mention only the more outstanding work since that time. Lucas *et al.*,[33] using the Palmer-Robscheit method, found 36 bloods on the first day averaged 117% (85 to 140%); 27 on the second, 114% (100 to 135%); 17 on the third, 110% (80 to 135%); 26 on the fourth, 114% (80 to 130%); 18 on the fifth, 107% (75 to 125%); 21 on the sixth, 113% (80 to 130%); 16 on the seventh, 109% (75 to 125%); 20 on the eighth, 103% (60 to 125%); and 17 on the ninth, 103% (90 to 115%). No standard

for their work is stated. They observed that sinus blood gave slightly higher readings than peripheral blood, although the differences were almost negligible, and that the hemoglobin averages of infants with icterus neonatorum were not reduced. In contrast to Schiff,[45] they found that tying the cord before and after cessation of pulsation had no effect on the hemoglobin after birth. Haden and Neff,[19] in a standardized study in which they took 15.6 gm. hemoglobin per 100 cc. of whole blood as 100%, used the ferricyanide method of Haldane and Van Slyke and venous blood. They found one 11-hour blood was 15.6 gm., 3 5-day bloods were 17.8, 16.2, 20.1 gm., one 6-day blood was 18.8 gm., one 8-day blood was 16.4 gm., and three 9-day bloods were 18.5, 19.2, 16.6 gm. Then Börner,[5] using the Huefner spectrophotometer and Bürker hemoglobinometer, studied 30 cases over a period ranging from 25 minutes to 15 days and obtained a distribution of hemoglobins from 15.2 to 23.71 gm., 22 of the cases having values above 18 gm.

Mitchell[38b] studied 69 cases and found that practically all infants showed a reduction in red cells and hemoglobin between the first and tenth days. He obtained hemoglobin averages of 120% (89 to 152%) on the first day, 114% (87 to 154%) on the third, 111% (76 to 148%) on the seventh and 106% (74 to 138%) on the tenth day. The blood values of both jaundiced and non-jaundiced infants fell to the same figure, although the total fall of the former was slightly greater. This was held by the author to be negligible. All other things being equal, he found that relative changes in weight exert an effect on the loss in red cells and hemoglobin. Mackay[34a,b] reported hemoglobin values of approximately 100% for infants during the first month, but later revised her values and reported 143% under 24 hours with a fall to 130% by the eighth day. She attributed the rapid fall to excessive destruction of the red cells. She observed that hemoglobin values are inversely proportional to the birth weights.[34b,c] Goldbloom and Gottlieb[15b] found the high hemoglobin level of the newborn to be related to the low oxygen tension of the blood of the fetus *in utero*, and using guinea-pigs showed that increasing the oxygen tension lowered the red count and caused a rise in blood bilirubin. This they thought to be due to a compensatory increased destruction of erythrocytes. Whitby and Hynes[56] found a mean of 151% at birth (range, 130 to 162%). Mugrage and Andresen,[39] using 13.8 gm. as standard, found 17.14 gm. for 40 newborns (range, 13.6 to 20.2 gm.) and a coefficient of variation of 8.6%. They found the differences between male and female infants to be negligible at this age. Andersen and Ortman[1] found 17.44 gm. of hemoglobin in the newborn (range, 12.7 to 24.85 gm.), using the Hellige universal colorimeter and 13.8 gm. as a standard. They also observed that a greater variability of values existed in infants as compared with adults. Guest, Brown and Wing[17] reported a hemoglobin average of 17.9 gm. for 24 samples

of cord blood, with a dispersion of 13 to 22 gm. They obtained a 1- to 10-day average for 89 cases of 19 gm., with a range of 14.5 to 25 gm. They utilized the Palmer carbon monoxide hemoglobin method, modified with a Wratten filter No. 74. Ross, Waugh and Malloy[42] found that in 7 cases the blood on the first day averaged 110% while by the fifth day these same infants showed 90% hemoglobin. Another series of 41 cases on the fifth day averaged 109% (Palmer method).

Observations. Using the Evelyn photoelectric technique and considering 15.6 gm. hemoglobin per 100 cc. blood as equivalent to 100%, we obtained an average hemoglobin of 15.36 gm. in 52 umbilical bloods with a dispersement of 11.86 to 18.72 gm. On the second day, 45 samples from the fontanel averaged 15.49 gm. (range, 11.23 to 19.66 gm.). On the fourth day, the average of 46 infants was 15.46 gm. (range, 11.86 to 19.34 gm.). By the sixth day, the average of 39 samples was 14.93 gm. (range, 11.86 to 18.72 gm.). On the ninth day the average of 39 cases was 14.70 gm. (range, 11.86 to 17.94 gm.). In order to determine whether the presence of anemic infants had materially changed the general averages, we broke down our data into 20% with the highest hemoglobins, the 20% with the lowest hemoglobins, and the intermediate 60% and compared them with the averages for all cases. It is readily seen (Table 1) that the 60% group is nearly identical with the average of all cases, so that no definite influence by a minority of low readings is exercised.

TABLE 1.—HEMOGLOBIN AVERAGES OF ALL CASES COMPARED WITH THE SELECTED GROUPS. GRAMS/100 CC. BLOOD.

Time.	No. of cases.	Averages all cases.	Averages 20% high.	Averages 60% mid.	Averages 20% low.
Cord blood . . .	52	15.36	17.02	15.37	13.70
2d day	45	15.49	18.11	15.30	13.45
4th day	46	15.46	17.74	15.37	13.51
6th day	39	14.93	17.11	14.88	12.87
9th day	39	14.70	16.95	14.66	12.73

In our series, 30% of the infants developed clinical icterus. Of these 18 newborns, all but 5 developed jaundice on the fourth day. The others became jaundiced on the second, third and fifth days. The average hemoglobin of 16 cord bloods of infants who later developed jaundice was 15.07 gm., while the remaining non-icteric infants averaged 15.49 gm. The 15 samples from the second-day bloods on babies who later developed jaundice gave an average hemoglobin of 15.4 gm. with the non-icteric infants averaging 15.54 gm. On the fourth day, on which the majority became obviously icteric, 14 jaundiced infants averaged 15.3 gm., as against the 15.52 of the non-jaundiced group. By the sixth day, 13 icteric infants averaged 14.5 gm. and the non-icteric 15.13 gm. On the ninth day, 13 icteric infants averaged 14.35 gm. with the non-icteric at 14.85 gm. It will be seen that the greatest differences occur

after the fourth day, although the entire icteric group present a slightly lower hemoglobin average than do the non-icteric. The difference is, however, almost negligible and no correlation could be made between individual values and the appearance of jaundice. Table 2 is a comparison of data on jaundiced and non-jaundiced infants. The cord blood hemoglobin of a case of erythroblastosis was 11.86 gm., dropping to 11.23 gm. on the second, 10.78 gm. on the fourth, and 10.3 gm. on the sixth days. Another case on the third day had a hemoglobin of 8.4 gm., while one studied on the fourth day showed a value of 9.83 gm.

TABLE 2.—A COMPARISON OF HEMOGLOBIN, VOLUME OF PACKED RED CELLS, AND INDEX OF FRAGILITY AVERAGES BETWEEN JAUNDICED AND NON-JAUNDICED INFANTS. (NUMBER OF CASES AVERAGED IN PARENTHESES.)

Time.	Hemoglobin, gm. per 100 cc.		Vol. packed red cells in percentage.		Index of fragility.	
	Non-icteric.	Icteric.	Non-icteric.	Icteric.	Non-icteric.	Icteric.
Cord blood	15.49 (36)	15.07 (16)	51.4 (35)	51.1 (16)	405 (36)	390 (16)
2d day	15.54 (30)	15.40 (15)	49.8 (30)	48.8 (15)	350 (30)	338 (15)
4th day	15.52 (32)	15.30 (14)	49.2 (32)	47.7 (14)	324 (32)	335 (14)
6th day	15.13 (26)	14.50 (13)	47.7 (26)	45.1 (13)	333 (26)	346 (13)
9th day	14.85 (26)	14.35 (13)	46.5 (26)	44.4 (13)	344 (25)	379 (12)

In summarizing our findings on over 200 hemoglobin determinations on infants during the first 9 days of life, it is obvious that our results in no way agree with the extremely high figures which have been reported in the literature. There are, of course, several points which have to be borne in mind in this connection: first, the lack of definite data in many of the previous communications on the standards employed, making a true comparison difficult. Our determinations were all made in duplicate and read directly from the Evelyn colorimeter, which is known to be accurate to within ±2%, and reported in grams per 100 cc. whole blood. Secondly, there is the possibility of differences due to various geographic locations, for, as is well recognized today, this latter factor plays an important rôle in determining so-called normal figures for hemoglobin in adults and infants. In this connection, seasonal and climactic factors may be held partially accountable, for Wintrobe,[58b] in an extensive review, has pointed out that lower values are met with in the northern, colder regions. Our series of cases were all healthy, full-term infants of average birth weight, born between August 15 and October 1, but we did not follow the weight changes during the period of study. Nevertheless, it would appear that while there is an average variation from approximately 14 to 17 gm. (individual variation from about 11.5 to 19.5 gm.) of hemoglobin per 100 cc. of blood, the vast majority of children in Montreal are

born at this time with very close to 15.6 gm. of hemoglobin or 100%. Similar values are met with in blood taken from the fontanel on the second and fourth days.

During the 9-day period there occurs a gradual fall in the hemoglobin, which is equivalent to about 0.66 gm. or between 4 and 5% of the original total. This change is not noticeable until the fourth day, after which there is a definite decline, while an actual slight rise is noted on the second day. How great a rôle alterations in water content have to do with these changes is, of course, difficult to determine. The relation of hemoglobin to volume of packed red cells will be taken up in the next section with notes on probable influences. In inspecting the results of the individual infant, it was noted that some showed a constant hemoglobin level or slight rise, some showed a rather precipitous fall, while others (the majority) showed a delayed, slightly variable but constantly gradual decline in hemoglobin during the 9 days' period of study.

Table 2 clearly demonstrates that there is little, if any, appreciable difference between the hemoglobin figures of infants developing, and those not developing jaundice. Individually no relationship was found to exist between the total change in hemoglobin during the period studied and the appearance of clinical icterus. In our series, however, the babies with jaundice ran on the average a slightly lower figure with a slightly greater fall, but this difference would by no means appear sufficient to explain the jaundice on a basis of excessive blood destruction alone. Ross, Waugh and Malloy[42] have shown that such destruction is not the cause but probably that inadequate liver function is the main factor. Moreover, as will be shown later, no relation could be demonstrated in our series between the original height or the degree of fall in hemoglobin in relation to fragility of the red cells to hypotonic solutions. It is interesting that in the cases which developed icterus gravis neonatorum, due to erythroblastosis, the figures for hemoglobin were distinctly low from the first cord blood, which substantiates the view that the hemolytic process is well under way before delivery occurs.

Volume of Packed Red Cells. *Literature.* Wintrobe[58a] has emphasized the importance of using actual cell volume rather than the diameter of the cells, which have a variable thickness. This fact has been widely recognized and appreciated, so that the hematocrit has come into common use and further calculations concerning the cell have been derived from it.[58a,c–e] Mugrage and Andresen[39] reported an average of 53.18% (44 to 63.5%) for 40 newborn infants, with a coefficient of variation of 8.8%. They found the differences between male and female infants to be unimportant at this early age. Guest and Brown[16] reported 8 samples of cord blood and found a distribution of 42.9 to 69.1%. Ross, Waugh and Malloy[42] reported 7 normal non-icteric infants with a first day average of

58% and a fifth day average of 52%. Averages for 5 jaundiced babies were 59% on the first and 53% on the fifth days. Of 41 infants at 4 and 5 days who were not jaundiced, the average volume was 52%, while the average of a group of 22 jaundiced infants of the same age was 52.5%. Andersen and Ortman[1] studied 38 cases and obtained an average of 56.5% (42 to 78.5%) and a coefficient of variation of 14.78%.

Observations. In our series, the average volume of packed red cells for 51 umbilical bloods was 51.3% (range, 41 to 61%). On the second day fontanel blood the average volume for 45 samples was 49.15% (range, 37.5 to 62%). On the fourth day, the average of 46 samples was 48.7% (range, 35 to 63.5%). By the sixth day, the average of 39 samples was 46.8% (range, 36 to 60.5%). On the ninth day the averages of bloods from 39 infants was 45.9% (range, 35 to 57%). Again, in order to determine whether a few low values were greatly influencing the general averages, we calculated the averages for the 20% with the highest readings, the 20% with the lowest readings and the 60% intermediate (Table 3). It will be seen that the averages for all cases agree very closely with the values for the 60% intermediate group, so that we feel the frankly low values are to be expected and that they do not exert an untoward effect on our general data. It appears that at birth there is an average range in volume of packed red cells of approximately 45 to 58% (individual variation from about 35 to 64%), and that the average infant in Montreal is born with a volume of about 51%, or 8% greater than the normal adult figure.

As before, we grouped our infants into those with and those without jaundice and traced the changes in volume of red cells (Table 2). The 16 cord bloods of infants who later developed jaundice averaged 51.1%, while the non-icteric group averaged 51.4%. On the second-day venous bloods obtained by fontanel puncture, the 15 who developed icterus averaged 48.5%, as against the non-jaundiced group who averaged 49.8%. On the fourth day, the icteric group of 14 averaged 47.7% and the others 49.2%. This was the day on which the majority of infants became clinically jaundiced. On the sixth day, the 13 jaundiced babies showed an average volume of 45.1% and the non-jaundiced 47.7%. On the ninth day, the 13 jaundiced infants averaged 44.4% and the non-jaundiced 46.5%. Here again, the most obvious change occurs after the fourth day when icterus appears. We were unable, however, to observe any correlation between the original height and subsequent changes of individual values and the appearance of clinical jaundice. The case of erythroblastosis on which umbilical blood was obtained gave a volume of 37.2%, while on the second day it dropped to 34%, on the fourth day to 34% and on the sixth day to 30.5%. A third day sample of another case was 23.5%, while 1 fourth day case gave a value of 32%.

It is evident that our results are similar to those reported in the literature, although here again we are slightly lower in our averages. As clearly seen in Table 3, however, our figures are not influenced

TABLE 3.—VOLUME OF PACKED RED CELLS OF ALL CASES COMPARED WITH THE SELECTED GROUPS. (EXPRESSED IN PERCENTAGE.)

Time.	No. of cases.	Averages, all cases.	Averages, 20% high.	Averages, 60% mid.	Averages, 20% low.
Cord blood	51	51.3	58.1	51.1	45.1
2d day	45	49.5	58.0	49.2	41.7
4th day	46	48.7	56.4	48.5	41.9
6th day	39	46.8	55.1	46.7	38.8
9th day	39	45.9	53.1	45.9	38.5

by anemic infants and we feel these results to be a true picture for this locality. They are also in keeping with our hemoglobin values. However, in contradistinction to the delayed drop in hemoglobin which does not appear until after the fourth day, there is a continuous fall in the volume of packed red cells from the first day. This brings up the question of mean corpuscular hemoglobin concentration. If this is computed from the averages of all cases for each day it is found as follows: cord blood 30%, second day 31.3%, fourth day 31.8%, sixth day 31.9%, and ninth day 32%. It should be borne in mind that we are using 15.6 gm. of hemoglobin as normal for 47.5% volume of packed red cells and therefore 33% is our normal mean corpuscular hemoglobin concentration for adults (Wintrobe[58a]). It is quite apparent therefore that there occurs during this period a rise in hemoglobin concentration toward that met with in the adult. Guest, Brown and Wing[17] reported an increase in hemoglobin concentration after birth, while others have found the concentration constant throughout and to be similar to that met with in the adult.

It is obvious that several factors can and do play a rôle in the reduction of the volume of packed red cells without proportional reduction in hemoglobin. It is difficult, of course, to tell which plays the greater part and how much they may make closer correlation of both impossible due to their interrelationship and our insufficient understanding of them. Loss of fluid from the cells could account for the fall in volume without a corresponding fall in hemoglobin, and we believe this to be quite possible. The introduction of new and smaller cells with higher hemoglobin concentration would have some influence in this same connection. Previous investigators are in agreement that the red cells at birth are larger than those found in the adult, and that they decrease in size during the first week. Börner[5] reported an average diameter of 8.63 μ at birth but stated that no change was observed during the first 15 days. Mitchell[38b] later found a decrease in cell volume from 109 to 104 cu.μ in the first 10 days, while Saragea[44] reported a fall in diameter from 8.6 to 8.3 μ in the first 10 days. It naturally

follows that the volume of packed red cells will vary with the size of the cell measured.

Physiologic destruction of the cells, of course, has no small rôle in the reduction of both the hemoglobin and the volume of packed red cells. Recently Josephs[25] has advocated a decrease in cell formation as an additional cause of the fall, which continues over the first 3 months of life. He believed this to be substantiated by the fact that the reticulocytes were diminishing in spite of blood loss. There was no appreciable increase in the total urobilin excreted. Furthermore, administration of iron did not prevent a fall in hemoglobin. Changes in weight have been shown to influence the results, so that rapid increases cause a more rapid fall in blood values, and conversely retarded gain or a loss results in a slower fall. Dehydration, when of a sufficient degree to manifest itself clinically, exerts a marked effect. Another important factor is that of changes in total blood volume, concerning which little work has been done on humans under the age of 1 year. Bawkin[2] showed that there is a decrease in plasma water during the first 3 to 4 days, but observed the water content to be quite variable in the infant and subject to sudden changes. Later Bawkin and Rivkin[3] showed that the volume of blood and plasma in infants is higher in relation to body weight and varies more widely than in adults. They demonstrated that the volume of packed red cells paralleled changes in total blood volume; hence a fall in hemoglobin is due to reduction in circulating cells and not to an increase in plasma volume as some had supposed. We did not carry out blood volume determinations, although we realized the importance of such a study. It is of interest in this connection to observe that Gibson and Evelyn[14] have recently devised an exceptionally accurate photoelectric colorimetric technique for such determinations.

We found a lower average volume of packed red cells for the jaundiced infants, as compared with those not developing icterus, the difference not being appreciable until after the sixth day, when it reaches 4%. We feel, however, that this difference is negligible and will demonstrate our reasons in the forthcoming paper on blood bilirubins. Furthermore, we were unable to demonstrate any relationship between the total change in volume of cells during the period studied and the appearance of clinical jaundice.

Reticulocytes. *Literature.* Krumbhaar[30a,b] found that reticulocytes reach a maximum of 5% in the first 24 hours of life and are about 3% thereafter until the end of the first week, when they reach normal adult levels of less than 1%. Friedlander and Wiedemer[13] reported 11% reticulocytes in the first 24 hours, the number steadily and uniformly decreasing to the eighth day, when it reaches adult values. Frank[12] demonstrated that reticulocytes of the newborn are 1 to 9% during the first week. Seyfarth[46] announced a 5 to

10% range within the first few hours with a fall to 0.3 to 1% in 6 days. Seyfarth and Jurgens[47] later reported 7% at birth, 2% in 10 days, and 0.7% by 3 weeks. Kato[26] gave 1.4 to 1.9% with a maximum of 5.5% and a minimum of 0.1% during the first 36 hours with a fall to 0.5% after 5 days. Goldbloom and Gottlieb[15] found 7% reticulocytes in umbilical blood, 5% on the second day, 3% on the third day, 2% on the fourth and 0.5% on the fifth days. They were practically absent by the sixth day.

Observations. On 41 examinations of the umbilical blood, we found an average of 2.7% (range, 0.2 to 5%). On the second day venous blood, the average of 34 samples was 3.1% (range, 0.3 to 4.5%). On the fourth day, the average of 28 cases was 2.3%, with a distribution of 0.3 to 4.2%. One examination carried out on the fourth day blood of a case of erythroblastosis was 10.6%. On the sixth day 24 samples averaged 1.2% (range, 0.2 to 3%), while on the ninth day the average of 22 cases was 0.34% (range, 0.1 to 0.9%).

Fragility. *Literature.* A brief review of the outstanding literature pertaining to the fragility of the red blood cells of the newborn gives a picture which varies from decreased to normal to increased resistance of the cells to hemolysis. In adults, hemolysis normally begins in the 0.44 to 0.48% solution and is complete in the 0.34 to 0.4% solution. No one, of course, has published material which has been determined by our method so that we are unable to compare closely our results with similar reports from other investigators. Van de Velde[52] found increased resistance of the erythrocytes in human fetal blood. Hofmeier[22] as early as 1882 reported that in adults blood mixed with a 0.25% saline solution showed no red cells remaining, while in newborns the cells were still numerous. He decided after further observation that the resistance of the cells in the first days of life was increased and that by the fourth day had begun to decrease. A greater resistance of the erythrocytes in the newborn than in the adult was reported by Hawksley and Lightwood,[21] Hornung,[23] Unger,[51] and Viola.[53] Simmel and Simmel-Rapp[49] found an increased resistance in newborn children which simulated that met with in marked and long-continued jaundice of the adult. In the newborn, they found that one-third of the cells remained in the 0.3 solution while one-half to three-quarters remained in the 0.4 solution, and no hemolyzed cells were present in the 0.6 and 0.7 solutions. They observed that the resistance of the cells increased during the first week in children with or without clinical jaundice and that no definite difference between the jaundiced and non-jaundiced could be demonstrated during the first and second weeks. They felt, therefore, that jaundice of the newborn is in no way accompanied by a lowered resistance (increased fragility) of the red blood cells. They observed a fall in resistance beginning the

second week, with normal values obtained by the fourth week. Pollitzer[41] reported that in normal infants as well as in icterus gravis neonatorum, the fragilities were variable.

The same resistance in the newborn as in the adult was found by Knöpfelmacher,[28] Mensi,[36] and more recently by Cserna and Liebmann,[8] and Mitchell,[38] the latter reporting hemolysis with a range of 0.55 to 0.52% to 0.32 to 0.25%. Slingenberg[50] found the same resistance but observed an increase in the newborn during the first 4 days which remained higher than in the adult until after the tenth day. In contrast to this, a lessened resistance was found by Cathala and Daunay,[7] Maliwa,[35] and Klima and Rosegger,[27] who noted that reticulocytes were especially less resistant. In this connection Goldbloom and Gottlieb[15] reported "a marked increase in the fragility of red corpuscles in cord blood. The same increase in fragility was found in the peripheral blood of infants. The resistance returns to normal or above normal at the end of about 1 week. An increase in the number of immature red cells, reticulated forms and nucleated red cells was found in the cord blood and in the peripheral blood." The disappearance of these immature forms with return of the fragility toward normal was taken by them to mean that the reticulocytes were the cause of the increased fragility noted at birth. Other workers have been unable to demonstrate this, while Sabrazes and Leuret[43] consider the reticulocytes to be especially resistant towards hemolysis. Mermod and Dock[37] observe that the reticulocytes and young cells resist hypotonic saline unusually well although they are more fragile toward saponin and oxalate or citrate solutions.

Anisohemolysis—the increased span of hemolysis from maximum to minimum solutions—was observed by Jona,[24] Whitby and Hynes[56] and Hallez,[20] the latter reporting an average initial hemolysis in the 0.56% solution. Carr[6] found an average range of 0.45 to 0.28% (maximum, 0.5%; minimum, 0.2%), and also pointed out an increased breadth of hemolysis. Simmel and Simmel-Rapp[49] made similar observations.

Observations. Using the method of Waugh and Asherman and the Evelyn colorimeter, we carried out fragility tests in conjunction with the previous work. Taking 400 as the average normal adult index of hemolysis and 350 to 450 as the normal range, we calculated the resistance of the red blood cells of the infants. On 52 samples of umbilical blood, we obtained an average index of 400 (range, 280 to 528). On the second day, 45 samples of venous blood gave an average index of 346 (range, 224 to 429). On the fourth day, the average index of 46 cases was 328 (range, 222 to 414). On the sixth day, the average index of 39 infants was 337 (range, 234 to 441). On the ninth day, 37 cases averaged 356 (range, 246 to 471) (see Chart 1).

We felt it best to express our results according to the 20% with the highest indices, the 20% with the lowest indices (greatest resistance) and the 60% intermediate. Chart 1 shows these averages

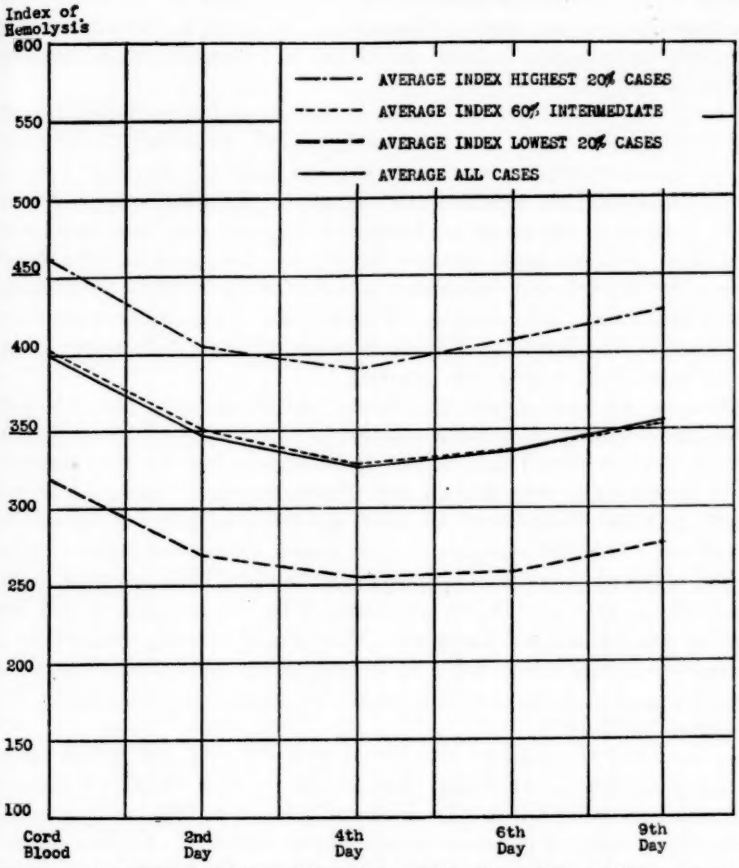

CHART 1.—Averages of indices of hemolysis during the period studied comparing selected group values with averages of all cases.

plotted against the averages for all cases; details are given in Table 4. Here again the 60% intermediate group presents values which are nearly identical with the average for all cases and rules out, we

TABLE 4.—INDICES OF HEMOLYSIS OF ALL CASES COMPARED WITH THE SELECTED GROUPS.

Time.	No. of cases.	Averages, all cases.	Averages, 20% high.	Averages, 60% mid.	Averages, 20% low.
Cord blood . . .	52	400	466	404	320
2d day	45	346	409	351	269
4th day	46	328	389	330	257
6th day	39	337	415	337	260
9th day	37	356	432	355	280

believe, any marked influence which can be exerted by very high or very low values present in a minority of cases. It is of interest to observe in connection with the determination of the fragilities, that a separate hemoglobin determination is made at the same time the tubes are set up, and in this manner we have a check upon our previous hemoglobin values which were obtained by a slightly different method.

It will be noted that the index of hemolysis for cord blood is at the normal adult figure and there occurs a fall in the index signifying an increased resistance on the second and again on the fourth days, from which point a gradual rise occurs to the ninth day. At no time is there evidence of an increased fragility and the variations met with between high and low figures are the same as have been shown by Waugh and Asherman to exist in the adult. As regards individual cases, it is worthy of note that not a single exception occurred in the character of these changes, the only differences being in the level from which they started.

Because we were aware that hemolysis of the cord blood would take place readily in oxalate solutions,[15,37] we marked those bloods which were received and slight hemolysis noted in the plasma. Only occasionally was this an appreciable amount, inasmuch as we made our determinations as soon after withdrawal as possible. However, of the 52 samples of cord blood, 18 showed some degree of hemolysis at the time of carrying out the tests. The average index for these cases was 438, as compared with the average of 383 for the 34 non-hemolyzed samples. This would slightly reduce to a more correct figure the index of hemolysis on cord blood, but does not change the general character of the curve, as will be seen by referring to Chart 1.

In dividing the infants into those who did and did not develop jaundice (Table 2) we found that of the 16 cord bloods of infants who later became icteric the average index was 390, as compared with the average of the non-jaundiced cases of 405. On the second day, 15 samples of fontanel blood of infants who became jaundiced averaged 338 while the others averaged 350. On the fourth day, the 14 infants who were jaundiced averaged 335, while the non-jaundiced infants were 328. By the sixth day, the 13 jaundiced infants showed an increase in index to 346, with the non-icteric at 333. On the ninth day, 12 samples from icteric infants averaged 379, while the non-icteric was at 344. In Chart 2 the indices of hemolysis in the two groups of icteric and non-icteric infants are plotted separately against the general averages. It will be noted there is no evidence that icteric infants show an increased fragility. However, the finer detail of change which is brought out by this method does show that in the babies developing jaundice there is an earlier cessation of fall and more rapid return toward normal levels. This may be due in some way to the hyperbilirubinemia. In addi-

tion, 1 case of erythroblastosis on which four determinations were made showed an index of 542 on the umbilical blood, 496 on the second day, 479 on the fourth day, and 454 on the sixth day. A case studied on the third day showed an index of 547 with hemolysis extending throughout all the solutions. Another case studied on the fourth day gave an index of 439. In all these cases there is increased

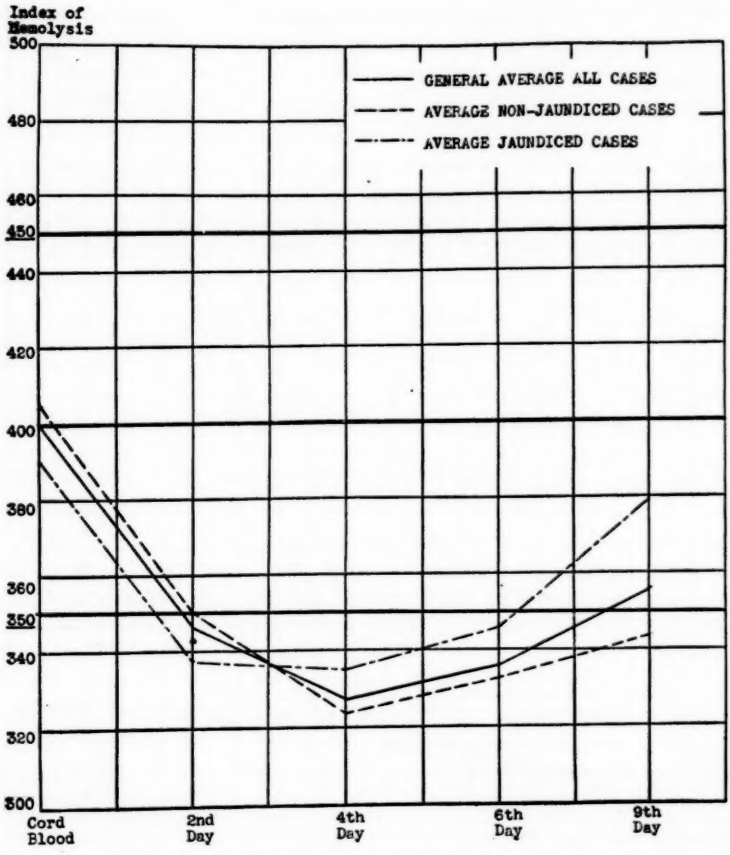

CHART 2.—Comparison of average indices of hemolysis of jaundiced and non-jaundiced infants with general averages during the period studied.

fragility of the red cells which, however, in the first instance shows a tendency to return toward normal.

In order to illustrate the amount of hemolysis in the various dilutions and thus the character of the fragility curve (hemolygram) which is not shown by the hemolytic index, we have compiled Chart 3. In this, the composite curves for each day studied are compared with the average of 50 adults. This clearly demonstrates the anisohemolysis which is present at this age period and which

has been previously reported.[6,20,24,48,49,56] By this is meant that the erythrocytes show an abnormal spread in the dilutions at which they hemolyze, so that one finds a certain number of cells which are unusually resistant and others which are abnormally fragile. This type of curve is a common finding in many hypochromic anemias

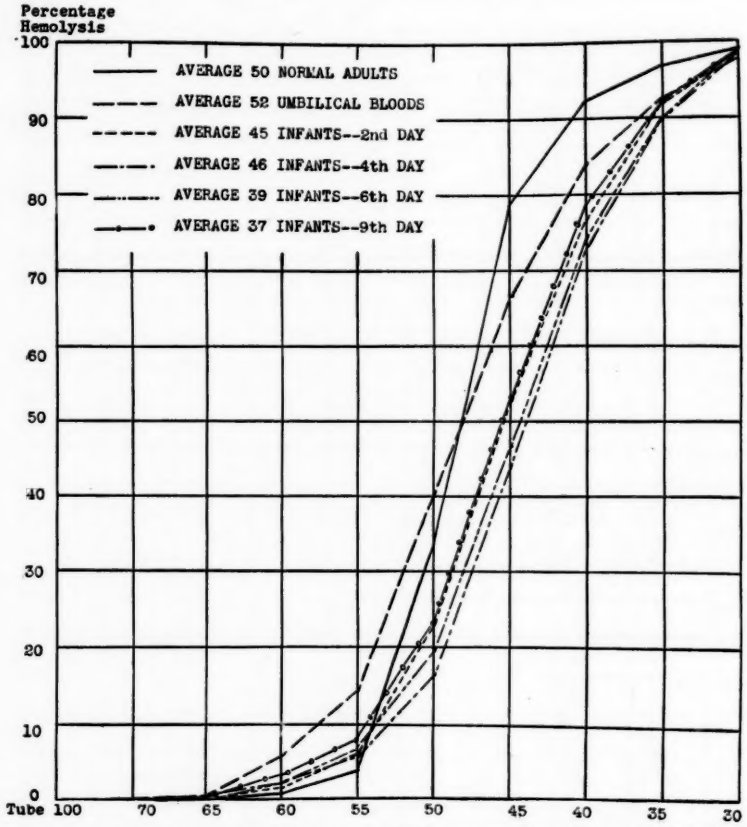

CHART 3.—Comparison of erythrocyte fragility curves (hemolygram) of newborn infant bloods (umbilical, 2nd, 4th, 6th, 9th days) with 50 normal adult males.

of the adult. A similar chart which is not reproduced here showed no difference in the character of the erythrocyte fragility curves in the icteric and non-icteric infants.

In comparing the indices of fragility with the hemoglobin values, no relationship could be demonstrated. At birth, for example, the 20% of umbilical samples with the highest indices (least resistance) had an average hemoglobin of 15.9 gm., while the 20% with lowest indices (greatest resistance) had an average of 15.61 gm. Individually, the widest variations were observed and no prediction as to fragility of the cells could be made from hemoglobin values.

Comment. We have studied some of the blood changes in 60 infants during the first 9 days of life. Our results for hemoglobin and volume of packed red cells are lower for the most part than those generally noted in the literature. We believe that several factors may account for this apparent discrepancy, namely, geographical location, season and climate, and the absence of a standard technique employed by some workers. We have utilized an improved and accurate photoelectric colorimeter hemoglobin technique. Our infants were all full term and within the limits of usual birth weights. The decrease in hemoglobin and volume of packed red cells which we observed during the period of study we believe to be caused primarily by the physiologic destruction of the erythrocytes which takes place during this period. At the same time, we quite appreciate that there are various other factors which are bound to affect the results obtained. These are changes in water content of the cell, changes in blood volume, diminution in size of the cells and, quite possibly, decrease in erythrocyte formation. In this connection, it is of interest to note that we observed an increase in mean corpuscular hemoglobin concentration during the period studied, so that by the ninth day the value was nearly that of adults in this region.

Although our infants who developed clinical icterus showed on the average slightly lower values than did those who failed to develop jaundice, the two groups changed in about the same degree during the 9 days, and we feel that on the whole the differences are negligible. In this connection we believe the distinction between icteric and non-icteric infants on the basis of clinical jaundice to be a deceptive one, but further observations and discussion will be reserved for our next paper which concerns detailed indirect and direct blood bilirubin determinations.

In regard to the fragility of the erythrocytes, we have definitely shown that at birth the index of hemolysis in the newborn is essentially the same as that in the adult, and moreover exhibits a similar individual variation. A fall (increase in resistance) then occurs which continues until the fourth day at which time it has reached a value definitely below that of the normal adult. A gradual rise then occurs which, however, by the ninth day has not as yet attained its original level.

In the studies of the hemolysis curve it is demonstrated that a characteristic type of anisohemolysis is present. This indicates that some unusually resistant and other unusually fragile cells persist throughout the period studied. In the case of infants developing clinical icterus, the changes in resistance of the cells are essentially the same as as in the non-icteric, with the exception that there is a slightly earlier cessation of fall and a more rapid return of the resistance toward normal levels. We believe our results on changes in hemolysis during this 9-day period, because of the more

exact methods at our disposal, are particularly conclusive, and exclude any possibility that icterus neonatorum is referable to an increased fragility of the erythrocytes.

Summary. 1. The average total hemoglobin of newborn infants in Montreal at birth is about 15.6 gm. (100%), and falls 0.66 gm. (5% of the original value) within the first 9 days of life.

2. The average volume of packed red cells in newborn infants in this locality is 51.3% (108% of our normal adult's figure), and falls 5.4% (10.5% of the original value) in 9 days.

3. As the decrease in hemoglobin and volume of packed red cells are not identical, it is apparent that the mean corpuscular hemoglobin concentration rises (from 30 to 32%) during the first 9 days, approaching the concentration of adults in this region.

4. The average figures for hemoglobin and volume of packed red cells in infants developing clinical icterus are only slightly lower than in the non-icteric group. No correlation could be demonstrated between the original height or subsequent changes in individual values and the appearance of clinical jaundice.

5. Reticulocyte estimations are similar to those found by other investigators.

6. The fragility of the erythrocytes in newborn infants as determined by the hemolytic index is normal at birth. The index falls, indicating a greater resistance, during the first 4 days, after which it returns toward normal.

7. The erythrocyte fragility curves demonstrate a constant and characteristic degree of anisohemolysis throughout the period studied.

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STUDIES ON CIRCULATION IN PREGNANCY.

IV. Venous Pressure Observations in Normal Pregnant Women, in Pregnant Women With Compensated and Decompensated Heart Disease and in the Pregnancy "Toxemias".

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Conflicting reports as to the value of the arm venous pressure in normal pregnant women appear in the literature (Table 1). One-half the studies report the arm venous pressure as normal;[4,7a,13,14,18] the other half report the venous pressure to be high during normal pregnancy.[2,6,11,19,23] There has been little study of the venous pressure in either compensated or decompensated heart disease during pregnancy. Extremely high venous pressure values have been reported in the pregnancy "toxemias"[11,19] but certain considerations, to be discussed later, cast doubt on these findings.

The general plan of study outlined previously[7a] has, where possible, been followed, that is, repeated observations were made on the *same* patient at frequent intervals throughout pregnancy and during the puerperium. In venous pressure studies, as in other investigations of the circulation in pregnancy,[7,a,b,20,21,22] such a plan of study is most important for the satisfactory understanding of the behavior of hemodynamic changes since variations between different individuals at the same phase of pregnancy may sometimes be greater than changes occurring during the entire pregnancy period in the same individual. This plan of study has been difficult to follow in the toxemic and decompensated cardiac patients except in the few cases in which either toxemia or cardiac failure happened to develop in patients who were already being studied. Hence, in the study of these groups most of the cases were first studied after the complications leading to investigation had developed. Such patients were then usually studied throughout the remainder of pregnancy and in the puerperium.

Methods of Study and Sources of Error. Arm venous pressures were determined according to the direct method of Moritz and von Tabora.[16] The skin at the site of venipuncture was anesthetized with 2% procaine without adrenalin. The zero point of the manometer was placed, with the aid of a level, at the reported level[16] of the right auricle, *i. e.*, a point 5 cm. dorsal to the junction of the fourth costochondral junction and the sternum, with patient in the supine position. Normal saline was used to fill the apparatus. Actually, the measurements were made in centimeters of normal saline though, as is customary, reported in centimeters of water. All observations were made with the patients fasting and after at least 20 minutes bed rest.

The lowest of at least three determinations which checked each other within 0.5 cm. of water and were satisfactory observations (free flow of saline from manometer, no evidence of extravenous injection, no signs of obstruction, immediate response to obstruction of vein) was taken as the reading for that particular day.

As the literature reveals such conflicting results (Table 1), it is important to consider the *sources of error* in the determination of the venous pressure. Consideration of them includes:

TABLE 1.—ARM VENOUS PRESSURE IN NORMAL PREGNANT WOMEN. SUMMARY OF LITERATURE.

Observer.	Year.	Method.	No. of cases.	No. of observations.	Results.
Runge[18]	1924	Direct	22	22	Normal
Kaboth[11]	1924	?	?	?	High
Carulla[6]	1926	Indirect	30	30	High
Villaret[23]	1930	Indirect	9	9	High
Krukenberg[13]	1932	Direct	29	29	Normal
Barath and Weiner[2]	1933	?	11	11	High
Strauss[19]	1935	Direct	20	20	High
Cohen and Thomson[7a]	1936	Direct	10	41	Normal
Landt and Benjamin[14]	1936	Direct	19	?	Normal
Burwell[4]	1938	Direct	22	46	Normal

1. The use of an "indirect" method is believed to be a source of error as it has been demonstrated[3] that the "indirect" method, when used to determine venous pressure at levels lower than 20 cm. is quite unreliable.

2. It is important that the patient rest quietly for the period of time mentioned above and remain relaxed during the test. Insufficient preliminary rest, and "tenseness" (incomplete general relaxation) lead to erroneous high values which return to lower levels if the examiner awaits relaxation.

3. Internal rotation or abduction of the arm may result in falsely high readings. They also may occur unless there is adequate support to hand and forearm (incomplete local relaxation) on the side in which the needle is inserted. The use of small pillows or a hand-rest as support may overcome this source of error.

4. Readings should not be made until enough time has elapsed for saline in manometer to reach its level. The test is not complete if manometer level is falling, even though slowly. A sound practice is to take as the answer the lowest of three readings, all of which check within 0.5 cm. H_2O.

5. Obesity, in certain individuals, leads to high venous pressure readings.[17]

6. During pregnancy the breasts are large and during the last months may cause venous obstruction to arm veins with falsely high venous pressure in the arms, particularly if the patient is in the supine position. In some cases, if the breast or its axillary attachments are shifted slightly by the examiner, there is an immediate fall in venous pressure to a correct lower level, which level may be checked repeatedly. This is believed to be an important source of erroneous high readings in late pregnancy, reflecting temporary venous obstruction and not that of the generalized venous pressure (right auricle).

7. Contractions of the uterus are followed by rise in venous pressure, of sometimes as much as 10 cm. The patient is not conscious of all uterine contractions (Braxton-Hicks) which occur in late pregnancy and may last ½ minute or more. Unless the examiner palpates the abdomen in cases where there is high reading, he cannot be sure that he is not reporting the transient effect of uterine contraction on the venous pressure, rather than the actual venous pressure for that patient. For instance, in Case 223, venous pressure was observed over ½ hour's time to remain constant at 6.7 cm. H_2O. However, on several occasions during examination, it rose abruptly to levels of 12, 14, and 16 cm. and returned, after an interval of about 1 minute, to the level of 6.7 cm. H_2O. Palpation over the uterus revealed definite uterine contraction corresponding to the increased venous pressure. Uterine relaxation corresponded with the return of venous pressure to the lower level, where it remained until another contraction. The patient was completely unaware of these contractions.

The likelihood of error, then, is greatest during the final months of pregnancy, when the breasts are large, the patient has difficulty in maintaining a comfortable position in bed, and the uterus is undergoing Braxton-Hicks contractions. It is of interest to note that it is during this period that high venous pressures have been reported by some observers for normal pregnant women.[11,19]

Various limits for normal venous pressure have been set by investigators.[8,10,[illegible],23] For this study, 12 cm. H_2O was regarded arbitrarily as the upper limit of "normal."

Results. The material for this study comprises venous pressure observations on 20 normal pregnant women, 27 compensated cardiacs, 18 decompensated cardiacs and 21 "toxemics."

I. Normal Pregnant Women. On 20 normal pregnant women 94 observations (65 before, 29 after delivery) were made (Table 2). The antepartum values varied between 2.5 and 10 cm. H_2O, average 7.2; the postpartum observations between 3 and 12 cm. H_2O,

average 7.3 cm. H_2O. All the values were within limits for normal non-pregnant women.

The individual and average venous pressure values were slightly higher in early pregnancy than in mid and late pregnancy and the puerperium (Table 2, Fig. 1). The average venous pressure after

TABLE 2.—THE ARM VENOUS PRESSURE IN 20 NORMAL PREGNANT WOMEN.

Case No., Normal.	Weeks pregnant.								Weeks postpartum.		
	9–12.	13–16.	17–20.	21–24.	25–28.	29–32.	33–36.	37–40.	1–2.	3–6.	7–24
36	...	...	...	6.0	4.7	4.2	4.0	5.0	7.9	6.4	7.3
38	...	7.8	7.9	8.0	8.0	8.5	9.5	...	12.0	10.5	9.4
39	8.8	...	6.1	6.2	...	8.5	10.0	...	...	7.5	
40	...	6.0	6.7	6.1	7.0	6.9	6.8	...	...	6.7	
A	...	...	...	...	...	...	10.0	...	...	...	9.0
B	...	...	8.5	9.2	...	...	...	...	7.3		
C	7.8	...	...	...	9.4	8.0	...	...	7.0		
D	...	...	...	...	5.0	6.0	6.3	5.1	7.5	...	6.5
E	...	10.0	9.1	9.5	...	7.0	7.3	9.0	11.0		
F	...	...	...	6.3	6.2	6.5	7.0	5.5	7.0	...	6.5
G	...	...	..	...	11.3	9.8	9.1	8.7	9.0		
H	...	...	10.0	7.0	...	...	2.5	...	4.5		
I	...	...	...	5.1	...	5.5	...	6.0	...	3.0	
J	...	...	...	...	...	...	...	7.5	7.1		
K	...	...	...	6.0	5.5	...	7.5	9.5	8.0		
L	...	...	...	...	...	...	...	7.5	8.5		
M	...	...	...	...	...	...	...	6.5	7.5	...	7.7
N	...	...	...	...	6.5	...	5.5	6.9	...	6.5	
O	...	...	...	...	...	...	...	8.0	5.5		
P	...	...	...	...	...	...	...	7.5	7.3	6.5	
No. of observations	2	3	6	10	9	10	12	13	15	7	6
Average	8.3	7.9	8.1	6.9	7.1	7.1	7.1	7.1	7.8	6.7	7.7

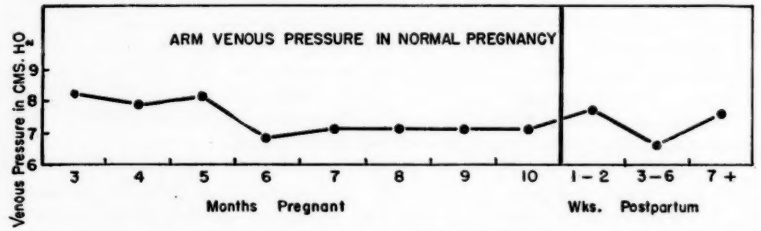

FIG. 1.—The arm venous pressure in normal pregnant women. (Average values based on 94 observations in 20 normal pregnant women.)

the sixth lunar month of pregnancy remained constant at just over 7 cm. H_2O until delivery. There was a slight average increase in the venous pressure in the puerperium as compared with the 21–40th week pregnant values. The late postpartum values are essentially the same as the early pregnancy values and are presumably close to the normal non-pregnant values for the group. In 9 of the 15 cases with observations before or during the second postpartum week the venous pressure was higher early postpartum than at the last antepartum observation, the average of the last pregnant values being 6.6 cm. H_2O, of the postpartum values 8.3 cm. H_2O.

II. A. Compensated Cardiac Patients. On 27 compensated cardiacs 144 observations (104 antepartum, 40 postpartum) were made. Of these patients 21 had rheumatic heart disease (19 Ms, 2 Ms, AR), 5 congenital heart disease (Table 3), 1 had RHD and hypertension. The antepartum values varied between 2.1 and 11.6 cm. H_2O, average 7.2; postpartum the range was between 2.5 and 10 cm. H_2O, average 7.2 cm. H_2O (Table 3).

TABLE 3.—THE ARM VENOUS PRESSURE IN 27 PREGNANT WOMEN WITH COMPENSATED CARDIAC DISEASE.

Case No., Cardiac.	Weeks pregnant. 9–16.	17–20.	21–24.	25–28.	29–32.	33–36.	37–40.	Weeks postpartum. 1–2.	3–6.	7–24.	Diagnosis.
31	...	...	...	...	...	9.1	7.1	...	8.1	9.5	Rheum. ht. dis., mitral stenosis
37	...	...	...	...	...	...	7.4	6.3	...	8.1	Rheum. ht. dis., mitral stenosis
39	...	...	...	...	...	...	5.8	...	8.9	...	Rheum. ht. dis., mitral stenosis
41	...	2.7	5.3	5.0	4.2	3.3	3.3	2.7	...	5.1	Rheum. ht. dis., mitral stenosis, aortic regurg.
46	...	...	...	...	10.5	8.0	...	4.1	...	...	Rheum. ht. dis., mitral stenosis
47	...	...	8.6	9.8	9.6	6.8	7.3	8.9	...	6.9	Rheum. ht. dis., mitral stenosis
48	...	...	...	...	...	9.3	8.5	7.0	6.1	...	Rheum. ht. dis., mitral stenosis
53	...	7.1	5.4	6.5	6.5	5.3	7.5	...	6.5	5.5	Cong. ht. dis., lesion?
55	10.0	9.5	9.9	10.0	11.8	...	...	...	10.0	9.0	Rheum. ht. dis., hypertensive ht. dis.
57	...	8.5	7.8	9.5	6.0	7.6	6.0	...	6.8	...	Rheum. ht. dis., mitral stenosis
64	...	7.3	8.8	11.4	11.5	10.5	9.8	8.0	9.0	...	Rheum. ht. dis., mitral stenosis
67	...	7.7	9.0	9.9	9.5	9.8	9.0	9.0	...	...	Rheum. ht. dis., mitral stenosis
70	...	6.3	8.1	8.1	8.0	8.5	8.5	8.5	...	...	Rheum. ht. dis., mitral stenosis
73	...	...	...	8.5	9.7	6.8	5.0	...	7.5	6.3	Cong. ht. dis., interventricular septal defect
74	...	4.5	4.7	3.0	3.5	2.2	2.1	...	5.0	7.5	Rheum. ht. dis., mitral stenosis
76	...	8.5	5.5	6.5	...	4.8	8.0	...	9.5	9.7	Cong. ht. dis., coarctation of aorta
77	...	...	...	...	...	3.5	4.2	3.1	...	...	Cong. ht. dis., interventricular septal defect
78	...	7.0	6.2	3.5	3.5	...	5.5	...	2.5	...	Rheum. ht. dis., mitral stenosis
88	10.0	9.5	9.5	...	9.0	7.5	7.0	8.8	...	...	Cong. ht. dis., patent ductus Botalli
87	8.5	7.5	9.5	...	8.0	9.0	...	...	10.3	...	Rheum. ht. dis., mitral stenosis, aortic regurg.
83	...	...	9.0	8.0	...	6.0	...	...	7.5	...	Rheum. ht. dis., mitral stenosis
84	...	...	5.5	6.0	...	5.8	5.5	8.0	...	...	Rheum. ht. dis., mitral stenosis
86	...	...	8.5	9.0	9.0	9.7	10.0	...	8.0	...	Rheum. ht. dis., mitral stenosis
85	...	...	...	...	...	...	8.5	...	9.1	6.5	Rheum. ht. dis., mitral stenosis
82	...	...	...	...	...	...	9.5	...	10.0	...	Rheum. ht. dis., mitral stenosis
90	...	...	...	...	...	...	8.5	...	6.8	...	Rheum. ht. dis., mitral stenosis
92	...	...	...	...	...	5.5	7.4	...	8.5	8.9	Rheum. ht. dis., mitral stenosis
No. of observations	3	12	16	15	15	20	23	11	18	11	
Average	9.5	7.2	7.6	7.6	8.0	6.9	6.5	6.8	7.2	7.5	

The individual observations and the average values showed changes throughout pregnancy and the puerperium similar to those observed in the normal pregnant group. There was a distinct tendency for the average venous pressure to diminish in the latter months of pregnancy and to return to the early pregnancy level in the puerperium (Table 3).

In venous pressure, as in blood volume[22] and circulation time,[7a] it is of interest to note that the compensated cardiac pregnant woman behaves exactly as the normal pregnant woman.

The type of heart lesion appeared to have no effect on venous pressure.

B. Decompensated Cardiacs. Sixty-four observations (47 antepartum, 17 postpartum) were made on 18 patients who developed heart failure during pregnancy. In all but 1 (Case 52, who developed paroxysmal nocturnal dyspnea) cardiac failure was of the congestive type. Persistent râles at the lung bases was the sole criterion

for heart failure in these patients.[5,15] In only 2 was there evidence of severe peripheral edema.

In the entire group there were 5 cases with pre-failure observations; in 12 post-failure observations were made; in 4 cases there were both pre- and post-failure observations and in 3 there was more than 1 observation when the patient showed evidence of heart failure. There were 24 antepartum observations made in the absence of congestive failure in patients who were to develop or had developed congestive failure. These values ranged from 3.9 to 10.5 cm. H_2O, with an average of 6.8 cm. H_2O. There were 23 observations made during failure, which ranged between 3.8 and 12.5 cm. H_2O with an average of 7.2 cm. H_2O (Table 4).

One patient developed heart failure in the 3d, 1 in the 4th, none in the 5th, 2 in the 6th, 6 in the 7th, 3 in the 8th, 4 in the 9th, and 1 in the 10th lunar month; none postpartum (Table 4). Seventeen postpartum observations on 11 patients who had showed unmistakable signs of congestive heart failure during pregnancy varied between 3.4 and 9.8 cm. H_2O, with an average of 6.1 cm. H_2O.

TABLE 4.—THE ARM VENOUS PRESSURE IN 18 PREGNANT WOMEN WITH CARDIAC DISEASE WHO DEVELOPED HEART FAILURE DURING PREGNANCY.

Case No., Cardiac.	Weeks antepartum. 9–12.	13–16.	17–20.	21–24.	25–28.	29–32.	33–36.	37–40.	Weeks postpartum. 1–2.	3–6.	7–24.	Diagnosis and remarks.§
43	...	...	...	...	...	...	7.7*	6.7	3.4	5.5	...	R.H.D., mitr. sten., aor. regurg., Ces. sect. at 39 wks.
45	...	...	...	5.2	3.9	5.7* 6.5*	4.5	4.0	4.3	...	...	R.H.D., mitr. sten., Ces. sect. at 39 wks.
50	...	7.7	7.1	8.7	9.9* 7.3*	6.7*	7.3	7.5	6.5	5.1	...	R.H.D., mitr. sten., preg. terminated at 35 wks.
51	...	8.0	4.8	7.0* 6.0*	7.0*	...	...	...	6.1	8.5	...	R.H.D., mitr. sten., Ces. sect. at term
52	...	...	6.4	5.7	6.9	7.0	7.3	4.9† 6.7	...	...	...	R.H.D., mitr. sten., aor. regurg., Ces. sect. at term. Pt. died 3 wks. postpartum of ac. bact. endocarditis
54	...	...	...	...	3.8*	...	...	...	...	...	...	R.H.D., mitr. sten.
58	5.7*	...	...	...	...	...	...	...	4.9	4.6	...	R.H.D., mitr. sten., preg. terminated at 26 wks.
61	...	...	...	3.9*	...	...	...	...	...	...	...	R.H.D., mitr. sten., Ces. sect. at term
63	...	...	...	...	...	...	5.5*	...	...	...	...	R.HD., mitr. sten., aor. regurg., Ces. sect. at 37 wks.
65	7.0	6.8*	...	...	...	...	...	...	5.7	...	6.5	R.H.D., mitr. sten., auric. fibril., preg. terminated at 16 wks.
71	...	...	...	...	12.5‡	...	...	...	...	...	...	Hypertens. ht. dis., "toxemia," Ces. sect. at 34 wks.
75	...	...	...	...	8.5*	...	...	8.3	6.5	...	7.0	R.H.D., mitr. sten., aor. regurg.
76	...	...	...	...	...	...	8.5*	...	...	7.5	...	R.H.D., mitr. sten.
78	...	...	...	...	...	...	9.0*	10.5	9.8	...	...	Cong. ht. dis., lesion?
94	...	...	...	...	...	7.5*	7.0	5.5	...	6.3	...	R. and cong. ht. dis., mitr. sten., patent duct. Bot.
96	...	...	...	8.0*	6.5	...	...	...	...	...	...	R.H.D., mitr. sten., pat. died undelv'd at 30 wks. of subac. bact. endocard.
98	...	...	...	...	...	...	...	5.0‡	5.0	...	...	Hypertens. ht. dis.
99	...	...	...	...	11.0*	...	...	...	...	...	...	R.H.D., mitr. sten , pat. died undelv'd at 31 wks. of ac. resp. infection and meningitis

R.H.D. = Rheumatic heart disease.
* Congestive heart failure.
† Paroxysmal nocturnal dyspnea (cardiac asthma).
‡ Congestive heart failure, "toxemia."
§ Unless otherwise noted patients delivered through the pelvis at term.

The type of cardiac lesion appeared to have no effect on the venous pressure. Although the venous pressure in these patients was within normal limits, except in 1 instance (Case 66, where there was massive edema), it is of interest to note that in 2 (Cases 45 and 50) where pre- and post-failure observations were made, the venous pressure was highest when there were signs of heart failure, although these values were not above the "normal" range (Table 4). In 1 (Case 51) with pre- and post-failure observations, clinical congestive failure was not accompanied by the highest observed venous pressure.

As compared with both normal pregnant women and compensated cardiacs, either individually or as groups, the value of the venous pressure even during congestive heart failure showed no significant difference. However, a non-clinic neglected case (No. 71) in whom congestive heart failure was advanced and was associated with considerable peripheral edema, showed the only venous pressure above normal encountered in the normal, compensated cardiac, or decompensated cardiac groups. Patients with heart disease who developed "toxemia" are discussed under "toxemia of pregnancy."

It is emphasized that all the cardiacs in this group were under careful supervision with restricted activity and weekly examination for signs of congestive heart failure or pulmonary congestion. The patients were hospitalized immediately when the earliest sign of heart failure, *i. e.*, constant râles at lung bases, appeared. These patients usually lacked symptoms of heart failure except fatigue and their dyspnea and edema were usually within the limits of normal pregnancy. Complete bed rest, diet, fluid restriction and digitalis constituted the hospital régime for these patients and venous pressure readings were usually made after 12 hours to several days of bed rest. Under these circumstances, as is known,[1] elevated venous pressure is not constant in mild congestive failure.

III. "Toxemias of Pregnancy." Seventy-four observations (50 before, 24 after delivery) were made on 21 pregnant women diagnosed "toxemia of pregnancy." The patients were grouped according to the classification of Reid and associates.[12] There were 8 patients (Table 5*A*) in Group A, *i. e.*, with evidence suggesting hypertensive disease independent of pregnancy. There were 13 (Tables 5*B* and 5*C*) patients in Group B, *i. e.*, with no evidence of hypertensive disease until the latter months of pregnancy; of these, 4 (Table 5*C*) showed eclampsia, the other 9 (Table 5*B*), preëclampsia. In the latter group there were, by chance, 3 patients who developed toxemia during the course of circulatory studies. The venous pressure values for the "toxemias" of pregnancy did not exceed 14 cm. H_2O, a value given[10] as the outside limit of normal. However, it can be noted on further inspection that more values fell in the upper normal range than in the non-toxemic pregnant group.

In Table 5*A* are presented data of the essential hypertension group. In addition to venous pressure data, there are charted obesity, maximum albuminuria and maximum blood pressure. The term "obesity" is reserved for patients who not only exceeded the average weight for their height, but in addition appeared "obese" to the casual glance. Patients over 200 pounds are indicated by ++. Albuminuria is recorded in terminology of the Massachusetts General Hospital.[24] Some of these patients had complicating hypertensive heart disease and others did not. The venous pressure level of patients in this group is slightly higher than that of the normal pregnant women. It is noted further, however, that the higher venous pressure values were all present in patients with obesity. In the 2 patients without obesity, the values were at the lower limits of normal. Since obesity[17] has been described as a cause for elevation of venous pressure, this association may be more than coincidental.

TABLE 5*A*.—THE ARM VENOUS PRESSURE IN PATIENTS WITH TOXEMIA OF PREGNANCY.

(Essential Hypertension Group—8 cases, 31 observations.)

	Weeks pregnant.						Weeks postpartum.						
Case No.	17–20.	12–24.	25–28.	29–32.	33–36.	37–40.	1–2.	3–6.	7–24.	Obes.	Max. alb.	Max. B.P.	Diagnosis and remarks.
201	...	...	...	5.0	...	...	...	6.0	...	0	T	220/140	Ess. hypertension, Ces. sect. in 35th wk.
202	...	...	...	10.5	10.5	8.5	...	8.0	...	++	T	230/140	Ess. hypertension, hypertens. ht. dis., amebic dys.
203	...	...	8.0	...	10.0	8.0	8.5	...	9.0	+	VST	148/108	Ess. hypertension
204	10.5	...	8.0	8.0	8.0	11.3	8.5	...	8.3	+	VST	170/104	Ess. hypertension
205	9.5	...	8.0	9.0	9.0	...	...	7.8	7.7	+	0	168/110	Ess. hypertension
206	...	...	...	7.5	8.5	...	...	...	...	+	T	170/100	Ess. hypertension
207	...	7.5	7.5	8.0	...	...	...	...	...	+	T	180/100	Ess. hypertension
208	...	...	...	...	3.1	...	5.0	...	...	0	T	180/110	Ess. hypertension, hypertens. ht. dis., card. decomp.

In the 9 preëclamptic patients described in Table 5*B*, it can be seen that most of the values fell within the upper normal range. A striking phenomenon in this group is that the venous pressure falls immediately postpartum. This contrasts with normal pregnancy[4] where a slight rise in venous pressure follows delivery (Table 2). In Case 212, venous pressure was 13 cm. H_2O. This reading was made while the patient was in severe congestive heart failure. There were moist râles throughout both lungs, there was massive edema and there had been a severe attack of cardiac asthma a few hours preceding the test.

Case Abstracts. Case 213 merits special attention as this was the only normal pregnant woman being studied who developed "toxemia." Her initial venous pressure was 2.5 cm. H_2O, the second venous pressure in the seventh month of pregnancy was 7.3 cm. H_2O. At this point blood pressure was normal, there was no edema, and no albuminuria. In the ninth month,

TABLE 5*B*.—THE ARM VENOUS PRESSURE IN PATIENTS WITH TOXEMIA OF PREGNANCY. (Preëclamptic Group—9 cases, 34 observations.)

TABLE 5B.—THE ARM VENOUS PRESSURE IN PATIENTS WITH TOXEMIA OF PREGNANCY.
(Preëclamptic Group—9 cases, 34 observations.)

Case No.	Weeks pregnant.							Weeks postpartum.						Diagnosis and remarks.
	10–16.	17–20.	21–24.	25–28.	29–32.	33–36.	37–40.	1–2.	3–6.	7–24.	Obes.	Max. alb.	Max. B.P.	
210				10.0 174/98 L.T. Ed.+				5.5 146/100 0 No Ed.	8.0 128/90 0 No Ed.		0	L.T.	174/98	Pre-eclampsia, severe. Del. by Braxton-Hicks version at 27 weeks
211					9.5 160/108 T. Ed.			8.3 130/90	8.5 130/90		++	T.	160/110	Pre-eclampsia , severe
212					13.0 148/110 L.T. Ed.			8.5 124/80 0 No Ed.	11.0 104/70 0 No Ed.		++	L.T.	166/110	Pre-eclampsia, severe; râles in chest; erythrobl. fetalis
213			2.5 130/80 0 No Ed.	7.3 120/70 0 No Ed.		7.0 170/100 L.T. Ed.+	8.0 140/90 L.T. Ed.	3.5 116/78 0 No Ed	4.3 110/72 0 No. Ed.		0	L.T.	170/100	Pre-eclampsia, severe; Ces. sect. at 36th week
214				11.0 156/102 L.T. Ed.+	11.0 138/104 L.T. Ed.+			9.0 120/80 S.P.T.			0	L.T.	166/110	Pre-eclampsia, severe
215							8.2 166/110 L.T. Ed.+				++	L.T.	166/110	Pre-eclampsia, severe; Ces. sect. at term; died of sepsis, 2 days later
Rheumatic heart disease complicated by pre-eclamptic toxemia.														
216			8.5 106/70 0 No Ed.	9.0 106/70 0 No Ed.	9.0 126/80 0 No Ed.	9.7 110/70 0	10.0 160/90 T. Ed.+		8.0 136/90 V.S.T.		0	L.T.	180/90	Pre-eclampsia, severe; rheu. ht. dis.; mitr. sten.
217	9.0 100/40 No Ed.		10.0 104/60 No Ed.	11.0 100/50 No Ed.		8.5 110/70 No Ed.	14.0 160/90 L.T. Ed.		5.9		+	L.T.	174/116	Pre-eclampsia, severe; rheu. ht. dis.; mitr. sten.; cong. ht. fail.
218					13.0 152/90 L.T. Ed.++			8.0 136/90 V.S.T.	8.3 94/60 0		+	L.T.	152/102	Pre-eclampsia, sèvere; premature separation of the placenta; rheu. ht. dis.; mitr. sten.

however, venous pressure was 7 cm. H_2O, blood pressure was 170/100 mm. of Hg, and massive edema and albuminuria had developed. In the tenth month, venous pressure was 8 cm. H_2O, there were edema, albuminuria, and hypertension and it was not until the postpartum period, when blood pressure was normal and edema was absent, that the venous pressure again returned to the low level observed before development of toxemia. The slight rise in venous pressure, in this case, preceded the development of clinical toxemia.

Cases 216 and 217 are cases of mitral stenosis who developed severe preëclamptic toxemia while being studied. In the first case there is no significant rise in venous pressure after the development of hypertension. In the second case, the development of hypertension and albuminuria in the tenth month of pregnancy was associated with edema, congestive heart failure and rise of venous pressure to 14 cm. H_2O. This is the highest value obtained in the entire study and is an example of congestive heart failure and preëclamptic toxemia developing in the tenth month of pregnancy in an obese woman. Following delivery, the venous pressure dropped to 5.9 cm. H_2O and the signs of congestive heart failure disappeared. Case 218, with a venous pressure of 13 cm. H_2O in the eighth month of pregnancy is another example of the combination of preëclamptic toxemia and mitral stenosis.

The eclamptic group, Table 5*C*, includes only 5 cases.

Case 221 was a 37-year-old woman who began having convulsions in the thirty-fourth week of her pregnancy. On the day of onset of convulsions and following 5 convulsions venous pressure measured 9.5 cm. H_2O, arterial blood pressure was 208/124 mm. of Hg, there was a large trace of albumin in the urine and marked edema was present. The patient was under influence of sedatives (sodium luminal, magnesium sulphate) at time studies were made. Two days later the patient was delivered and on the fourth day postpartum the venous pressure was 8 cm. H_2O and arterial blood pressure was 174/86 mm. of Hg. On the thirteenth day postpartum venous pressure was 7.5 cm. H_2O and arterial blood pressure was 142/82 mm. of Hg. This patient subsequently developed acute bacterial endocarditis and succumbed to it.

Case 222 had 1 convulsion. On the day preceding it the venous pressure was 6.3 cm. H_2O and the arterial blood pressure 210/120 mm. of Hg, there were râles in the chest and the observed vital capacity was 1700 cc. On the following day, 3 hours after her only convulsion, the venous pressure was 13 cm. of H_2O and arterial blood pressure 200/120 mm. of Hg. At time of study, the patient was quiet. She was delivered 31 hours later by the aid of a Voorhee's bag. Six weeks postpartum her venous pressure was 9.5 cm. H_2O, arterial blood pressure 152/98 mm. of Hg, the râles had disappeared from the chest and the observed vital capacity was 2930 cc.

Case 223 was a 23-year-old woman who was hospitalized because of the rapid development of edema and hypertension. She had gained 41 pounds in her pregnancy and 12 pounds in the eighteenth week, during which she was hospitalized. Studies at this time showed venous pressure of 6.7 cm. H_2O, arterial blood pressure of 167/94 mm. of Hg, marked generalized edema and a slight trace of albumin. The patient was delivered 3 days later and soon after delivery had one convulsion. Thirteen days postpartum the venous pressure was 7.1 cm. H_2O. All edema had disappeared and there was but a slightest possible trace of albumin in the urine. Case 224 was observed to have a venous pressure of 8 cm. H_2O 40 hours after the first convulsion. It can be seen from these data that slight, if any, elevation of the venous pressure occurs in coincidence with eclampsia. No measurements were made in any case during a convulsion. In Case 225, venous

TABLE 5C.—ECLAMPTIC GROUP—5 CASES, 10 OBSERVATIONS.

Case No.	Weeks pregnant.						Days postpartum.						Diagnosis and remarks.
	29.	29.	33.	34.	38.	40.	4.	13.	42.	Obes.	Max. alb.	Max. B.P.	
221				9.5 208/124 L.T. Ed.+			8.0 174/86 V.S.T.	7.5 142/82 S.P.T.		+	L.T.	230/128	9 convul. on same day as initial VP determination; died of bact. endoc.; cbr. accident
222	6.3 210/120 L.T. Ed.+	13.0 200/120 L.T. Ed.+							9.5 152/98 0 No Ed.	++	L.T.	230/160	1 convul.; râles at both lung bases
223					6.7 160/94 S.T. Ed.+			7.1 138/90 S.P.T. No Ed.		+	L.T.	170/110	2 convul.; VP observation 3 days before onset of convulsions
224						8.0 174/86 L.T. No Ed.				+	L.T.	210/110	5 convul.; died in "shock" 2 days postpartum; first convul. preceded by VP determination by 40 hrs.
225			5.5 174/104 L.T. Ed.+							0	L.T.	174/104	3 convul. 2 days before VP observation

Venous pressure is expressed in cm. H_2O. Presence of obesity indicated by +, marked obesity (200 or more lbs.) by ++, and absence of obesity by 0 in vertical column labeled "Obes." Maximum albuminuria during pregnancy is symbolized as follows: S.P.T. = slightest possible trace; V.S.T. = very small trace; S.T. = slight trace; L.T. = large trace[24]. Maximum arterial blood pressure during pregnancy expressed in mm. Hg. In Tables 5*B* and 5*C*, simultaneous data on venous pressure, arterial blood pressure, albuminuria and edema are given. Edema is denoted by Ed., marked edema by Ed.+, and no edema by No Ed.

pressure observation was made 3 days after the onset of convulsions. The patient was still undelivered. Albumin, hypertension, but a normal venous pressure were present.

Discussion. 1. *Control Values.* In addition to those studies made within 2 weeks after delivery, 13 observations were made on the normal group from 3 weeks to 6 months after delivery. These values, which were assumed to be the normal non-pregnant values for these women, ranged from 3 to 10.5 with a mean of 7.1 cm. H_2O and are similar to other normal figures in the literature.[10,16]

2. *Normal Pregnant Women.* The results of this study indicate that the venous pressure in normal pregnant women remains within the range of values for normal non-pregnant individuals. The discrepancy between these findings and those of observers reporting an elevated venous pressure[2,6,11,19,23] in normal pregnancy requires some explanation. The use of an indirect method by 2 of the observers[6,23] may have been a factor in their studies since it has been shown[3] that such a method is unreliable in determining venous pressure at levels under 20 cm. The other sources of error outlined may also have been contributory.

In 2 studies[2,11] the choice of method is not outlined. The paucity of observations makes analysis of the data impossible. In the other study[19] giving results at variance with those reported here (although the direct method was used), individual observations only were made, and then late in pregnancy when errors are so frequent. For these reasons the results cannot be accepted without reservation.

In contrast are the 5 other corroborative studies,[4,7a,13,14,18] where the venous pressure is described as being within normal limits. In each, the method of Moritz and von Tabora[16] or some modification[10,13] was used. In Studies 7*a* and 13 the observers report careful checking of individual observations.

Our study is lacking in observations on patients before pregnancy and also in the early months of pregnancy. More data should be obtained on the venous pressure in early pregnancy because, as suggested in another study,[14] and as indicated in the data of Tables 2 and 3, there seems to be a higher venous pressure in the early months of pregnancy than in the latter months. There is no conclusive explanation for this. A possible explanation, which however is at best speculative, concerns the increase in blood volume[22] occurring in early pregnancy and the increase in the superficial venous channels, as shown by the infra-red studies on the veins of pregnant women.[9] Is it not possible if the increase in blood volume early in pregnancy occurs rapidly that there may be a time lag before adequate venous channels develop, with a consequent early rise in venous pressure? The slight increase in venous pressure postpartum may be associated with lactation and in the infra-red vein studies made at this clinic[9] it was demonstrated that, whereas the abdominal veins receded postpartum, the veins over

the breasts and thorax became, if anything, more prominent. Venous pressure observations in the legs[4,18] have been reported as elevated in patients whose arm venous pressures were within normal limits. Our observations of femoral venous pressure, though scant, are corroborative.

3. *Pregnant Women with Heart Disease—Compensated and Decompensated.* Values for arm venous pressure in pregnant women with compensated heart disease were almost identical with those of normal pregnant women (Tables 2 and 3). This coincides with the usual finding that venous pressure is normal in compensated heart disease.[1]

In the group of cardiac patients with congestive failure the values remain within normal limits. In most cases persistent râles in the chest constituted the chief sign of failure. Marked peripheral edema was usually lacking. Venous pressure measurements, as well as clinical observations, then, support the general idea that so-called left-sided heart failure is the type to be expected in pregnancy. Despite occasional small increases in venous pressure (see Case 50) accompanying heart failure, the venous pressure is, unlike the vital capacity,[7b] of no value in the prediction or diagnosis of early heart failure in pregnancy.

In 3 cases of rheumatic heart disease, complicated by toxemia of pregnancy the highest venous pressure readings were recorded. Peripheral edema and albuminuria were present in all. Case 217, with obvious heart failure, showed a venous pressure of 14 cm. H_2O, the highest in the study, with a return to 5.9 cm. H_2O postpartum. This small amount of evidence adds to the clinical impression that toxemia of pregnancy may be an especially serious complication in the presence of organic heart disease.

4. *Toxemias of Pregnancy.* The number of observations in this group and their lack of complete consistence makes any broad conclusion from them unwarranted. However, certain points seem clear. These values do not corroborate the extremely high ones found by one observer[19] who found one-half of 20 values ranging from 13 to 21 cm. H_2O. Since this observer also found similar values in normal pregnant women and reports that he found in toxemics "a value not significantly different from normal pregnant women," it is difficult to compare his results with those presented in this study. Extremely high venous pressure readings were reported by another investigator[11] in 3 cases of eclampsia. This observer also reported high values in normal pregnant women. One of the cases reported by this observer showed an elevation of venous pressure above 50 cm., with marked fluctuations, with the values rising and falling rapidly. In this instance Braxton-Hicks contractions of the uterus were not ruled out as a possible explanation of the changes.

From this study it appears that, accompanying toxemia of preg-

nancy, there is apt to be a slight rise in venous pressure from the pretoxemic level, but that the rise is not an extreme one. The level of the venous pressure in no way correlated with the severity of the illness, the amount of edema or the arterial blood pressure. There is no crucial data in this study to indicate whether the slight rise in venous pressure contributes to form the edema, results from the edema, or is actually related to the edema. The drop in venous pressure immediately postpartum is an interesting difference from the usual trend in pregnancy.

There is no striking variation of the venous pressure in eclampsia in relation to the onset of convulsions. The highest values in venous pressure observed in this study were in patients with toxemia of pregnancy and previous heart disease.

Conclusions. 1. The arm venous pressure, as measured by the method of Moritz and von Tabora, is within "normal limits" during normal pregnancy.

2. This study corroborates the studies of others who find the venous pressure in normal pregnancy within normal limits and points out possible sources of error in those studies which report increase of venous pressure in normal pregnancy.

3. The venous pressure of normal pregnant women tends to diminish from early pregnancy to the sixth month, remains fairly constant throughout the remainder of pregnancy, rises slightly in the early puerperium and returns to the early pregnancy level later postpartum.

4. This same trend is present in pregnant women with compensated heart disease.

5. The measurement of venous pressure cannot be used to predict or diagnose early congestive heart failure in pregnant cardiac women.

6. There is probably a slight increase in venous pressure accompanying "toxemia" of pregnancy.

7. The venous pressure decreases immediately postpartum in patients with "toxemia" of pregnancy, in contrast to normal pregnant women in whom it usually rises.

8. This study does not corroborate the finding of extremely high venous pressures in "toxemias" of pregnancy.

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COR PULMONALE DUE TO OBSTRUCTION OF THE PULMONARY ARTERY BY SYPHILITIC AORTIC ANEURYSMS.

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It is well known that syphilitic aneurysms of the aorta which do not involve the aortic valve area may be present without evidence of heart failure, whereas aneurysms involving the aortic root with dilatation of the aortic valve ring frequently result in death from myocardial insufficiency. Such cases, presenting the clinical picture of aortic insufficiency, rarely offer any difficulty in diagnosis.

This communication points out a much more unusual way in which an aortic aneurysm may cause myocardial insufficiency, *i. e.*, by chronic compression of the pulmonary artery. Pressure upon the pulmonary artery is one of the less common complications of aneurysms of the aorta. The usual result in such cases is rupture of the aneurysm into the pulmonary artery. The dramatic and characteristic course of events in this phenomenon has been adequately described by Scott.[9] More rarely, however, the aortic aneurysm does not rupture but causes a chronic stenosis of the pulmonary artery. This burdens the right side of the heart, resulting in hypertrophy and dilatation of the right ventricle—the so-called *cor pulmonale*.

This combination of aneurysm and heart disease is very unusual and difficult to diagnose. The literature contains only scattered reports of its occurrence, notably those of Pollack,[5] Rindfleisch and Obernier,[6] Gairdner,[4] Arnold,[1] Bufalini,[2] Schlesinger,[8] Rohr and Ryffel,[7] Costa,[3] and Tibirica and Bittencourt,[10] most of which have

been particularly concerned with the anatomic findings. The following 3 cases are reported in order to direct attention to the clinical significance of this condition, *i. e.*, that compression of the pulmonary artery may be the cause of heart failure in those cases of aneurysm of the aorta in which involvement of the aortic orifice is not demonstrable.

Case Reports. Case 1.—H. H., a 57-year-old white carpenter, entered Cleveland City Hospital, January 9, 1938. His chief complaint was swelling of the legs of 4 months' duration. The patient had been in good health until 1935, when he began to have periodic attacks of pain in the chest. At that time fluoroscopic and film studies of the chest showed a large aneurysm of the first portion of the arch of the aorta. The transverse diameter of the aortic shadow measured 14 cm. in width (Fig. 1).

After antiluetic treatment the patient was in fairly good health until about September, 1937, when he developed shortness of breath, cough, swelling of the feet, weakness, and swelling of the abdomen. These symptoms became progressively more severe. Shortly before admission, he had had an attack of severe precordial pain, and subsequently had been very short of breath and acutely ill. He had had a penile chancre at the age of 18.

Examination showed the patient to be normally developed and fairly well nourished, but he was cyanotic, orthopneic, and acutely ill. The neck veins were markedly distended. There were râles at the bases; the liver was enlarged and tender; the abdomen contained fluid; and the trunk, genitalia and legs showed moderate pitting edema. The heart was enlarged and the cardiac mechanism was normal except for tachycardia. There was a systolic murmur of moderate intensity audible over the entire precordium. A tracheal tug was demonstrable, and there was a pulsating mass in the left upper chest. The blood pressure measured in millimeters of mercury was 130 systolic and 60 diastolic.

The blood Kline test for syphilis was 4+; the blood Wassermann test was negative. The urine contained albumin Grade 2.

The patient did not improve despite treatment and died on the third hospital day, January 12, 1938, of congestive heart failure. The clinical diagnosis was: 1, syphilitic aneurysm of the ascending aorta; 2, myocardial insufficiency, probably due to coronary artery sclerosis; 3, possible coronary thrombosis.

Autopsy. External examination was negative except for pitting edema of the legs and genitalia. The peritoneal cavity contained 300 cc., the right pleural space, 700 cc., the left pleural space, 900 cc., and the pericardial space, 200 cc. of serous fluid.

The *heart* weighed 425 gm. The right atrium and the right ventricle were dilated and hypertrophied, the ventricular wall measuring 0.7 cm. in thickness. In contrast the left atrium and ventricle were not significantly enlarged, the ventricular wall measuring 1.5 cm. in thickness. There was no narrowing of the coronary ostia and the arteries did not show noteworthy arteriosclerosis. There were no areas of infarction. The heart valves were normal.

The *aorta* showed a typical syphilitic aortitis with a large aneurysm involving the ascending limb and the adjacent portion of the arch. This aneurysm bulged forward and to the left in such a way as to compress the pulmonary artery. In fact, upon opening the pulmonary artery the wall adjacent to the aortic aneurysm was found to bulge into the lumen of the pulmonary artery (Fig. 2). The volume of the aneurysm was 800 cc. The aortic valves were competent when tested with a column of water in the aorta. There was no communication between the aneurysm and the pulmonary artery.

The *remaining viscera* showed chronic passive hyperemia.

FIG. 1 (Case 1).—Roentgenogram of the chest showing the aortic aneurysm.

FIG. 2 (Case 1).—The wedge points to the pulmonary artery which has been opened. The one wall of the pulmonary artery can be seen to bulge back into the lumen because of the external pressure caused by the aneurysm of the aorta. Note the increased thickness of the right ventricle.

Upon *microscopic examination*, the aorta showed syphilitic mesaortitis. The aortic leaflets were normal. There was evidence of hypertrophy of the right ventricle, and the various viscera showed chronic passive hyperemia.

The final diagnosis was: 1, syphilitic aneurysm of the ascending limb and arch of the aorta with compression of the pulmonary artery; 2, cardiac hypertrophy and dilatation, right side (cor pulmonale); 3, myocardial insufficiency with hydropericardium, pleural effusions, ascites, and chronic passive hyperemia of the viscera.

CASE 2.—S. W., a 41-year-old colored laborer, entered Cleveland City Hospital, May 31, 1930. His chief complaint was shortness of breath of 6 weeks' duration. The patient had been in good health until about April 15, 1930, since which time he had had shortness of breath, cough, edema of the feet, and weakness. The patient denied ever having had a penile chancre or rheumatic fever.

Examination showed the patient to be normally developed and well nourished but cyanotic and orthopneic. The jugular veins were distended. There were a few râles at the bases. The left border of the heart was at the anterior axillary line. The cardiac mechanism was normal except for tachycardia. There was a systolic murmur at the second intercostal space to the right of the sternum. The liver was not very tender, but was much enlarged, the edge being at the umbilicus. There was marked edema of the trunk, the genitalia, and the legs. The blood pressure measured in millimeters of mercury was 120 systolic and 90 diastolic.

The urine contained albumin Grade 1. The blood Wassermann test was 4+ on two occasions.

Fluoroscopic and film studies of the chest showed a marked enlargement of the heart, the total transverse diameter measuring 16.9 cm., whereas the total internal diameter of the chest measured 28 cm. The entire aorta was dilated with a definite aneurysm of the first part of the ascending aorta. The lungs showed passive hyperemia.

The electrocardiogram in the conventional leads showed a normal mechanism and right axis deviation.

The patient made temporary improvement with bed rest, digitalis, sedation, and diuretics but finally died of heart failure about 5 months after admission, on November 1, 1930.

The clinical diagnosis was: 1, syphilitic aortitis with aneurysm of the ascending aorta and narrowing of the coronary ostia; 2, cardiac hypertrophy and dilatation; 3, myocardial insufficiency.

AUTOPSY. External examination was negative. The *heart* with the aorta weighed approximately 600 gm. The enlargement of the heart was almost entirely right sided. The trabeculæ carneæ and papillary muscles were strikingly enlarged in the right ventricle and the chamber was markedly increased in size. The trabeculæ carneæ and papillary muscles on the left were of average size and the chamber was not enlarged. Otherwise the heart was normal. The aortic leaflets were normal. The coronary arteries and their ostia were normal.

The *aorta* showed a typical syphilitic aortitis. There was a saccular aneurysm 6 cm. in diameter, located 1 cm. above the commissures. This aneurysm contained a laminated, partially necrotic clot. Externally the aneurysm bulged forward and to the left compressing the pulmonary artery 2 cm. above the valve. The compression was severe and produced a marked stenosis of the pulmonary artery. There was no communication between the lumen of the aneurysm and that of the pulmonary artery.

The *other viscera* showed varying degrees of passive hyperemia.

Microscopic examination of the aorta showed the characteristic lesions of syphilis. Sections of the right ventricular wall showed hypertrophy. The other organs showed chronic passive hyperemia.

The final diagnosis was: 1, syphilitic aneurysm of the ascending arch of the aorta with marked compression of the pulmonary artery; 2, cardiac hypertrophy and dilatation, mostly right ventricle (cor pulmonale); 3, myocardial insufficiency with chronic passive hyperemia of the viscera.

CASE 3.—J. J., a 59-year-old white laborer, entered Mount Sinai Hospital November 18, 1931. His chief complaint was swelling of the legs of 1 month's duration. He had been in good health until about October 15, 1931, since which time he had had swelling of the legs and ankles, increase in size of the abdomen, and dyspnea on exertion. These symptoms had become progressively more severe. He denied any precordial pain but had had occasional sharp pains in other portions of the chest.

Examination showed the patient to be normally developed and obese, but acutely ill, severely dyspneic, and notably cyanotic. The entire body was edematous. The neck veins were markedly distended. There was dullness to percussion and diminution of the intensity of the breath sounds at both lung bases. The liver was enlarged, and there was moderate ascites. The heart was markedly enlarged in both directions. There was a systolic murmur at the apex and the mechanism was normal. There were no clinical signs of aneurysm of the aorta. The blood pressure measured in millimeters of mercury was 118 systolic and 90 diastolic.

Urinalysis showed albumin Grade 1. The blood Kline test for syphilis was positive.

Fluoroscopic study of the chest showed the heart to be enlarged to the right and the left, the transverse diameter being 16.5 cm. whereas the total internal diameter of the chest was 29.5 cm. There was considerable diffuse dilatation of the aorta, the transverse diameter measuring 9 cm. The lungs showed passive hyperemia.

The electrocardiogram in the conventional leads showed a normal sinus rhythm with marked right axis deviation. There was notching of the *QRS* complex in all leads.

The patient made temporary improvement on appropriate treatment, but ultimately expired on the 19th hospital day, December 6, 1931.

The clinical diagnosis was: 1, Ayerza's disease; 2, syphilitic aortitis with dilatation.

AUTOPSY. External examination was negative. The *heart* was considerably enlarged and dilated, weighing 630 gm. The right atrium was not appreciably hypertrophied, but the right ventricle was markedly hypertrophied, the wall measuring 10 mm. in thickness. The left atrium was normal except for dilatation. The left ventricle showed moderate hypertrophy, the wall varying between 10 and 20 mm. in thickness. The heart valves were normal. The coronary arteries and their ostia were normal.

The *aorta* showed syphilitic aortitis with a diffuse aneurysmal dilatation of the ascending limb, the circumference being 10.5 cm. The dilated aorta compressed the pulmonary artery for a distance of 3 cm. in such a fashion as to lead to a definite constriction of the pulmonary artery. The portion of the *pulmonary artery* cardiad to the stenosed area was dilated but nevertheless was thicker than usual, the wall measuring 2 to 3 mm. in thickness. The aorta showed no evidence of rupture.

The *remaining viscera* showed chronic passive hyperemia.

Microscopic examination of the aorta showed the typical changes of syphilitic aortitis. The aortic leaflets were normal. Section of the dilated portion of the pulmonary artery showed hypertrophy of the media. Elastic fibers were prominent.

The final diagnosis was: 1, syphilitic aortitis with aneurysmal dilatation and marked compression of the pulmonary artery; 2, cardiac hypertrophy and dilatation, mostly right ventricle (cor pulmonale); 3, myocardial insufficiency with chronic passive hyperemia of the viscera.

Comment. The following considerations are based on a study of the cases reported in the literature and the cases discussed in this communication.

Etiology. The cases were all presumably due to syphilis. This can be recognized from the gross description of the aorta in the older reports, and from the gross and microscopic findings in the more recent ones.

Frequency. All writers who have described this condition have commented upon its extreme rarity. No doubt the condition is very unusual but it is thought that the paucity of reports may be due to the fact that sufficient attention has not been directed to this entity.

The Aortic Aneurysm. These were located in the ascending arch of the aorta involving either the sinuses of Valsalva or the region just above the commissures. Their size was variable as is illustrated by the 3 cases here reported. In Case 1 the aneurysm was large, involving the entire ascending portion of the aorta and a portion of the arch. In Case 2 the aneurysm was relatively small, no dimension exceeding 6 cm. In Case 3 the aorta showed diffuse dilatation rather than a distinct aneurysm. Most of the cases in the literature describe relatively small aneurysms which brought about compression of the pulmonary artery more because of their location than their sheer size. In all cases the aneurysm bulged anteriorly and to the left, thereby encroaching upon the pulmonary artery.

The Pulmonary Artery. The pulmonary artery showed very definite obstruction in all cases. This was usually due, as in the cases here reported, to invagination of the wall of the pulmonary artery into its lumen. In a few recorded cases the obstruction was caused by a flattening of the pulmonary artery or by a viselike action caused by the aortic aneurysm. Uncommonly, the aorta eroded into the pulmonary artery and blocked its lumen, although there was not communication between the cavity of the aneurysm and the lumen of the pulmonary artery.

The Heart. All cases showed outstanding hypertrophy and dilatation of the right side of the heart, thus constituting in terms of modern terminology a cor pulmonale. None of the cases showed any significant lesion of the aortic valve. In one case the right ventricle was so dilated as to result in a relative tricuspid insufficiency.[6]

Clinical Findings. The aneurysm of the aorta was silent in some instances and in others gave clinical signs of its presence. The signs of myocardial insufficiency and especially of failure of the right side of the heart were evident. Cyanosis was a prominent feature in the cases in which the clinical findings were adequately described. Most of these cases showed a systolic murmur which was in no way diagnostic. Two authors[5,6] noted the presence of a systolic murmur heard over the back of the chest in the region between the scapulæ. One[5] felt that this murmur originated in the pulmonary artery at

the point of stenosis. Bufalini[2] described a systolic murmur and thrill located at the pulmonic area. This murmur was not noted in the cases here reported, although no particular search for its presence was made. In one case[6] (referred to above) there was clinical evidence of tricuspid insufficiency which at autopsy was found to be due to dilatation of the right ventricle and the tricuspid ring.

Roentgen Findings. Roentgen studies of the chest were made in only a few of the recorded cases. Except for indicating the presence of an aneurysm in such a location that pressure on the pulmonary artery could result, the roentgenologic findings were not unusual.

Electrocardiographic Findings. The only electrocardiograms available in this condition are the ones here reported. Both showed right axis deviation. On theoretical grounds it would seem that right axis deviation should be present almost invariably.

Clinical Course. In all cases reported the course was unfavorable and ultimately fatal.

Clinical Diagnosis. The possibility of an aneurysm causing heart failure by pressing on the pulmonary artery can be considered only if all other causes of heart failure are excluded. The likelihood becomes greater if signs of enlargement and failure of the right side of the heart dominate the clinical picture. Roentgen study is of help in showing that the aneurysm is in such a position that it can press upon the pulmonary artery. In certain cases, roentgenologic study might show enlargement of the right side of the heart. Electrocardiographic evidence of right axis deviation would be corroborative. Under such circumstances the diagnosis can be considered probable. In none of the cases in the literature or in those here reported was the correct etiologic diagnosis suspected antemortem.

Summary. Heart failure due to syphilitic aortic aneurysms is usually caused by dilatation of the aortic valve ring with resultant aortic insufficiency. Heart failure due to obstruction of the pulmonary artery from pressure of a syphilitic aortic aneurysm is an extraordinary occurrence. Three such cases and similar ones previously reported permit the following conclusions:

1. The aortic aneurysm may be large or small. It bulges anteriorly and to the left, thereby compressing the pulmonary artery.

2. The pulmonary artery is obstructed by either simple pressure, a viselike action, or by erosion of the aneurysm into the lumen (without rupture).

3. The heart shows hypertrophy and dilatation of the right side thus constituting in terms of modern terminology a cor pulmonale.

4. Clinically, myocardial insufficiency, especially of the right side of the heart, is evident. The aneurysm may or may not give physical signs of its presence. Roentgen studies show the aneurysm in such a position that it could press on the pulmonary artery and the electrocardiograms reported show right axis deviation. Under such

circumstances and if all other causes of heart failure are excluded, the diagnosis can be considered probable.

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A STUDY OF THE INCIDENCE OF CORONARY OCCLUSION AND ANGINA PECTORIS IN THE WHITE AND NEGRO RACES.

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Most studies of the incidence of coronary occlusion and angina pectoris have failed to emphasize the relative frequency of these conditions in the white and negro races.[2,5,10,13] White[19] states that "race, temperament, social and economic status, and occupation appear to have some slight bearing on the incidence of coronary disease," and "the full-blooded negro rarely or never" has angina pectoris. Levy[12] states that in coronary heart disease there is no significant difference in the incidence in the white and colored races, although in his own expereince the more advanced degrees of sclerosis are less common in the negro. These two observers, however, fail to mention the relative racial incidence of coronary occlusion *per se*. On the other hand, in those series where the relative racial incidence was studied, striking differences were noted. Schwab and Schulze,[16] in a study of 4252 white patients, found 11 cases of angina pectoris, while a study of 3936 negro patients failed to disclose a single instance of this condition. Hedley,[7] in a study of 450 fatal cases of heart disease in Washington, D.C., found 34 instances of coronary thrombosis, all being white (30 males and 4 females). Gager and Dunn,[4] in a study of consecutively chosen records of 1200 cases (white 600, negro 600) of structural heart disease in Washington, D. C., found 20 instances of angina pectoris and 15 of coronary thrombosis in the white group, while in the colored series there were 10 instances of angina pectoris and 2 of thrombosis. Lisa and Ring,[14] in an analysis of 100 necropsy records, selected from

942 necropsies performed at City Hospital, New York, from 1928 to 1931, found a racial incidence of 81 white persons (66 males, 15 females), 18 negroes (16 males, 2 females), and 1 Chinese male. Stone and Vanzant,[17] in a study of 915 consecutive cases of heart disease seen from 1920 to 1926, found 501 to be white and 414 negroes. In this group, angina pectoris occurred in 15 white patients (10 males, 5 females) and in 6 negro females. These authors make no reference to coronary occlusion. Laws,[9] in a review of 438 patients (white, 237; negro, 201) with arteriosclerotic and hypertensive heart disease, found 16 instances of angina pectoris in the white and 3 in the negro. There was no mention made of coronary occlusion. Johnston,[8] in a study of 400 consecutive autopsy records, 100 for each sex of each race, found 13 instances of coronary occlusion in the white (9 males and 4 females) and 6 in the negro (4 males and 2 females). The author made no reference to angina pectoris. The lack of sufficient emphasis on the incidence of coronary occlusion and angina pectoris in the white and negro races prompted us to investigate this subject.

Methods and Materials. Our observations were made at Charity Hospital, an institution well adapted for such a study because the admissions of the two races are practically equal. This study includes a review of the case records of patients admitted to the medical services during the last 10 years (1928–1937, inclusive). There were 137,514 medical admissions during this period, of which 83,231 were white and 54,283 were negroes. Only those records were selected which fulfilled the following criteria:

I. *Coronary occlusion was considered present when:* A. Patients presented the classical history and had had 1 or more of the following manifestations: 1, moderate fever and leukocytosis of short duration; 2, changing electrocardiogram; 3, pericardial friction rub. We have chosen to refer to this group as patients *diagnosed by clinical methods.*

B. *Patients had classical electrocardiographic evidence of coronary occlusion.* These patients will be referred to as the group *diagnosed by electrocardiographic methods.*

C. *Occlusion was found at autopsy.* We referred to this third group as those *diagnosed by autopsy.*

II. Angina pectoris was considered present when the patient presented a history of the classical pain which was relieved dramatically by nitrites.

As a result of the rigid diagnostic criteria, some cases of angina pectoris and coronary occlusion were probably discarded. Nevertheless, in order to obtain significant conclusions, we felt that this was justified, since we were reviewing case histories.

Results (See Tables 1 and 2). *Coronary Occlusion.* We found 162 acceptable records of definite coronary occlusion. Of these, 138 (85.2%), were white (121 males and 17 females) and 24 (14.8%) were negroes (22 males and 2 females). Of the white patients, 44 were diagnosed by clinical methods, 54 by electrocardiographic evidence and 40 by necropsy. Of the negro patients, 2 were diagnosed by clinical methods, 2 by electrocardiographic evidence and 20 by autopsy. In both races the occlusion occurred most frequently during the fifth, sixth and seventh decades. Included with the

white patients is a case of a 56-year-old Indian male who had a posterior infarct.

TABLE 1.—THE RELATIVE INCIDENCE OF CORONARY OCCLUSION IN THE WHITE AND NEGRO RACES.

Race.	Sex.	Age.							Method of diagnosis.							Season.				Total.
										E.C.G.		Autopsy.								
		30 to 39.	40 to 49.	50 to 59.	60 to 69.	70 to 79.	80+.	Total.	Clinical.	Ant.	Post.	Ant.	Post.	Both.	Unknown.	Autumn.	Winter.	Spring.	Summer.	
White*	M	8	30	43	31	9	0	121	37	27	23	10	3	3	18	31	39	23	28	138
	F	1	2	5	7	2	0	17	7	3	1	3	0	0	3	6	5	2	4	
Negro	M	2	7	7	5	0	1	22	1	1	1	7	0	1	11	3	8	6	5	24
	F	0	2	0	0	0	0	2	1	0	0	0	0	0	1	1	0	1	0	
Total																				162

* One of the patients included in the white group is a 56-year-old Indian male.

Angina Pectoris. There were 29 (90.7%) cases of angina pectoris in the white race (24 males and 5 females) and 3 (9.3%) in the negro (3 males and 0 females). The greatest incidence of angina pectoris occurred in the sixth decade.

TABLE 2.—THE RELATIVE INCIDENCE OF ANGINA PECTORIS IN THE WHITE AND NEGRO RACES.

Race.	Sex.	Age.							Season.				Total.
		30 to 39.	40 to 49.	50 to 59.	60 to 69.	70 to 79.	80+.	Total.	Autumn.	Winter.	Spring.	Summer.	
White	M	3	4	9	6	2	0	24	5	10	4	5	29
	F	2	1	0	1	0	0	5*	2	2	0	1	
Negro	M	0	1	2	0	0	0	3	0	2	1	0	3
	F	0	0	0	0	0	0	0	0	0	0	0	
Total													32

* Includes 1 white woman whose age was unknown.

Discussion. In the past, the difference in incidence of coronary occlusion in the negro and white races has not been stressed. In fact, some observers state that there is no significant difference.[13,19] Many studies of coronary occlusion fail to include an analysis of

racial differences.[5,10,11,20] The studies of Hedley[7] and Lisa and Ring[14] suggest a relatively low incidence of coronary occlusion in the negro. These findings may be questioned because of the failure of the observers to make allowances for the relatively small negro population where the studies were made. The findings of Gager and Dunn[4] and Johnston[8] are corroborated by our studies: we found 138 white patients and only 24 negroes with coronary occlusion (see Table 1). When a correction is made for the difference in the medical admissions for the 2 races, we obtained a ratio for coronary occlusion of 7 whites to 2 negroes. These findings tend to be significant, as the cases were selected under similar circumstances with practically equal negro and white admissions.

In contrast to the above differences of opinion in regard to coronary occlusion, the observers uniformly agree that the incidence of angina pectoris in the negro is rare.[9,16,17,19] We found this to be true in our studies. We were able to collect 32 cases of angina pectoris, of which 29 were white and 3 negro (see Table 2). In no instance was angina pectoris found in the negro female. We eliminated those patients in whom luetic aortitis was suspected. Of the 32 patients with angina pectoris only 1 had a positive Wassermann. Subsequent clinical and laboratory observations failed to disclose any signs of aortitis in this patient.

Any explanation for the low incidence of coronary occlusion and angina pectoris in the negro can only be conjectured at this time. Coronary occlusion and angina pectoris, along with other cardiovascular states such as hypertension, have been associated with high tension living conditions and occupations requiring considerable responsibility and intelligence, *e. g.*, the physician, banker and lawyer. However, it has been shown recently in the South that hypertension is more prevalent in the negro than in the white,[1,15,18] while coronary occlusion and angina pectoris are uncommon. Likewise, as pointed out by Schulze and Schwab[15] and Weiss and Prusmack,[18] it is doubtful that the American negro is as placid and phlegmatic as is commonly supposed. An evaluation of the effect of nervous tension on these conditions becomes more difficult when one considers hypertension in the African, as contrasted with the American, negroes. Civilization probably has had its effect upon the nervous state of the American negro, producing greater nervous tension than is found in the African. Hypertension is rare in the latter and very common in the former, while the incidence of coronary disease is relatively low in both.[3] These conflicting observations cast doubt upon the significance of psychogenic factors influencing the incidence of coronary occlusion and angina pectoris in the white and colored races.

Physical effort apparently has no effect upon the difference in incidence of these diseases in the two races, for the patients in our series were laborers who, as a rule, did equally strenuous work. These

findings, however, are in contrast to those of Levine and Brown,[10] who state that physical effort is conducive to coronary thrombosis, although they did not mention a racial difference. It is interesting to note that physical effort was essentially the same in both races of our series. However, angina pectoris, a syndrome precipitated by physical effort, was rarely observed in the negro. This suggests that, although physical effort is significant as a precipitating cause of the pain of angina pectoris, it apparently is of little importance as a primary etiologic factor. The low incidence of coronary occlusion and angina pectoris in the female, as compared to the male, might be considered as evidence favoring the idea that physical effort is conducive to the occurrence of these conditions. This is open to question, however, as there probably are unknown factors of sex relationship not associated with physical effort influencing the incidence.

As mentioned by Weiss and Prusmack[18] in their studies of the incidence of hypertension, the relatively low incidence of angina pectoris in the negro as compared to the white may be partly explained on the basis of the following factors: 1, the lack of intellectual ability to interpret fully and describe the sensation of pain; 2, the distress of myocardial, cerebral or renal failure symptoms, which often obscures all history of angina pectoris; and 3, the fact that uncomplicated anginal type of heart failure usually occurs in an ambulatory patient. It is doubtful, however, that such factors could account for more than a small part of the difference between the 2 races. It is more than likely that there is a genuine difference in racial incidence, the cause or causes of which might throw light upon a more thorough understanding of the etiology and pathogenesis of angina pectoris as well as coronary occlusion.

Summary. A study of the medical case histories at Charity Hospital of Louisiana from 1928 through 1937 revealed a relatively low incidence of coronary occlusion and angina pectoris in the negro as compared with the white race. Of 162 instances of coronary occlusion, 138 (85.2%) were white (121 males and 17 females), and 24 (14.8%) were negro (22 males and 2 females); of the 32 instances of angina pectoris, 29 (90.7%) were white (24 males and 5 females) and 3 (9.3%) were negro (all males). After the data were corrected for the differences in admission, the ratios of white to negro for the incidence of coronary occlusion and angina pectoris were found to be 7 to 2 and 4 to 1, respectively. Some of the factors which might influence the incidences of the two diseases in the white and negro races were discussed.

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EXPERIMENTAL LOCALIZED AURICULAR NECROSIS.

An Electrocardiographic Study.*

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Auricular electrocardiographic changes occurring in coronary disease have been studied by a number of investigators, and altered auricular complexes of this type have been seen from time to time in electrocardiograms in the Heart Station files. Master[7] reported changes in the *P* wave in 32 of 40 cases of acute coronary artery occlusion. These changes consisted of increased amplitude, notching or widening and were attributed to auricular dilatation. Inasmuch as the changes occurred most frequently in Leads I and II, left auricular dilatation was presumed to be the cause. Lambert,[5] in correlating similar electrocardiographic findings in patients with experimentally induced auricular infarction in rabbits, concluded that such changes were the result of impaired auricular coronary circulation comparable to those in ventricular coronary insufficiency. Vela[13] reported a case with inversion of the auricular complex during an attack of angina pectoris followed by a return to normal contour after the attack. Condorelli[2] was unable to obtain alterations in the configuration of the auricular complex or the *P–Q* interval by temporary occlusion of the ascending auricular branch of the right coronary artery. Analysis of the records of Parkinson and Bedford[10] dealing with ventricular *S–T* changes in coronary thrombosis shows notching, inversion and abnormal amplitude of the *P* wave. Regnier and Lambert[11] reported 3 cases of acute ventricular infarction in which inversion, reduplication and diminution in the *P* waves occurred. Abramson, Fenichel and Shookhoff,[1] in an experimental study on dogs and cats, observed elevation of the auricular *S–T* segment in Lead I in cases of circumscribed necrosis of the left auricle, and depression of the same segment in right auricular

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necrosis. Depression of this segment occurred in Leads II and III without regard to the location of the necrotic area. In a case of arteriosclerotic heart disease with complete heart block, Nathanson[9] has observed an auricular complex in Lead III consisting of a deep auricular Q wave, an elevation of the auricular S–T segment with upward convexity and an upright T_a wave, comparable to changes occurring in the ventricular complexes in coronary thrombosis. Feil and his associates[3,4] have reported careful postmortem studies of 10 cases of auricular infarction. The right auricle was involved in 2; auricular fibrillation with frequent ventricular extrasystoles was noted in 1, and sinus rhythm, sinus arrest, ventricular escape, and a prolonged P–R interval was seen in another. Maher[6] observed a thrombus in the right auricle involving the region of the sinus node in a case of coronary sclerosis presenting sino-auricular block. This brief survey of the pertinent literature indicates that auricular coronary insufficiency and infarction do occur and may be associated with changes in cardiac rhythm and in the contour of the auricular complex.

This study was undertaken to observe the effect of experimentally induced circumscribed auricular necrosis upon this complex in an effort to gain further insight into the mechanisms responsible for its occurrence.

Method. Auricular necrosis was induced in 57 areas of 22 dogs by the intramural injection of 95% alcohol. Of these, 6 were induced in the left auricle; 16 in the left auricular appendage; 24 in the right auricle; and 9 in the right auricular appendage. Inasmuch as localized appendicular necrosis yielded results similar to necrosis of the auricle proper, the designation of right and left auricular necrosis will be used in all cases. The injections in 37 areas were preceded by the mechanical induction of A–V block, which enabled detailed comparison of the auricular S–T segment and auricular T wave. The Meakins[8] method of inducing A–V block was used: 2 blades of a clamp were introduced into the heart on either side of the interventricular septum and the common A–V bundle was clamped. The usual limb leads were used, at times with a sensitivity of the string greater than customary. In addition, an esophageal lead was used, the electrode being placed in the esophagus at the level of the auricle. A No. 1 Hindle string galvanometer was used. Control records before and after application of the clamp were obtained in each case prior to the induction of the circumscribed necrosis. All tracings were obtained with the chest open and the pericardium removed.

Results. Of the 20 instances of induced auricular necrosis not preceded by the induction of A–V block, changes occurred in 10, 7 resulted in a nodal rhythm; 1 in a paroxysmal auricular tachycardia; and 2 in a wandering pacemaker. These arrhythmias resulted from localized necrosis of the right auricle in the region of the sinus node.

Of the 37 produced following mechanical A–V block, changes occurred in 30; 2 resulted in intra-auricular block represented by unusually tall, broad, slurred and notched auricular complexes

(Fig. 1). These resulted from involvement of the left auricular appendage at its cephalic margin and point of junction with the auricle proper near the interauricular septum. Of the remaining 35, particular attention was given to the auricular S–T segments and T waves. Outstanding changes, which occurred in 28, were elevation of the S–T segment with upward bowing similar to changes occurring in the equivalent segment of the ventricular complex in ventricular wall infarction. This was associated with the development of an auricular Q wave in all instances.

The observation that of 14 left auricular areas of necrosis producing such auricular S–T changes, 10 resulted in an elevation of this segment with upward bowing in Lead I, with an associated auricular Q wave (Fig. 2, *a*, *b*) aided in localizing the necrosis. At the same time a depression of the auricular S–T segment occurred in the other leads. In 4 other instances the same type of change, more marked in degree, occurred in the esophageal lead with minimal changes in the other leads (Fig. 3). In the 14 cases of right auricular involvement which produced auricular S–T deviations, Lead I was not so affected. The S–T changes appeared in Leads II and III, and quite markedly in the esophageal lead in all cases (Fig. 4). In these instances, the changes were similar to those occurring in Lead I with left auricular necrosis. Inverted auricular T waves in Lead I occurred in 2 cases soon after localized left auricular necrosis (Fig. 5) without previous S–T elevation.

In the auricular initial complex (P proper) changes frequently consisted of diminution (in 18) or increase in its amplitude (in 8), combined with slurring (in 9), notching (in 9), broadening (in 3), inversion (in 7), and the development of a Q wave in 28 and a broad S wave in 5. Except for the correlation regarding the Q waves mentioned above, changes of these types could not be correlated with the location of the necrosis. An M or W shaped initial auricular complex appeared in Lead I after left auricular necrosis in 1 instance, and in the third and esophageal leads after right auricular necrosis in another.

LEGENDS FOR FIGS. 1 AND 2.

FIG. 1.—(*a*) Control, esophageal lead, E, and Lead III. (*b*) Intra-auricular block shown by prolongation of P wave with gross slurring and decreased amplitude resulting from localized necrosis in left auricular appendage, cephalic margin, near junction with left auricle proper and near interauricular septum. (Mechanical A–V block induced prior to control record.) Standardized 1.5 cm. = 10 millivolts.

FIG. 2.—(*a*) Control, esophageal and three standard leads. (*b*) Development of auricular Q and elevation of auricular S–T with upward bowing in Lead I, resulting from localized necrosis of left auricle. (*c*) One hour later, apparent evolution with loss of auricular Q_1, development of auricular Q in Leads II, III and esophageal lead, inverted auricular T_1, elevation of auricular S–T in Leads II, III and esophageal lead. (Mechanical A–V block induced prior to control record.) Standardized 1.5 cm. = 10 millivolts.

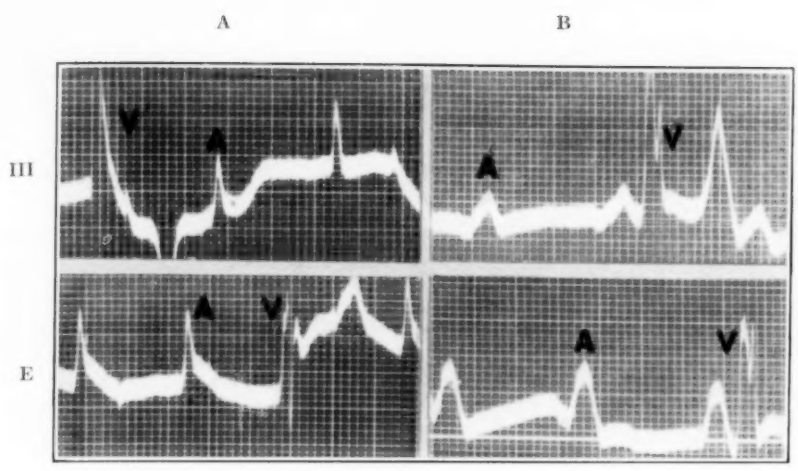

FIG. 1

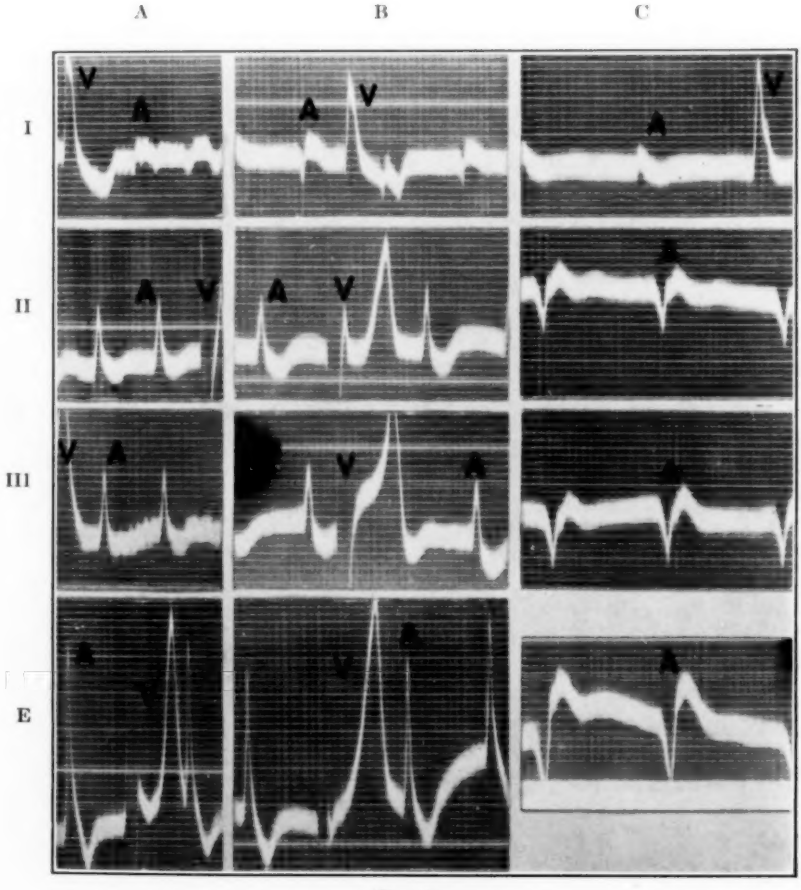

FIG. 2

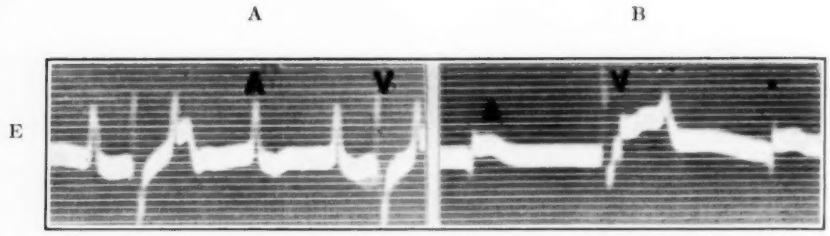

FIG. 3.—(*a*) Control, esophageal lead. (*b*) Development of auricular Q, elevation of auricular S–T with upward bowing, resulting from localized necrosis of right auricle. (Mechanical A–V block induced prior to control record. Standardized 1 c.m. = 10 millivolts.

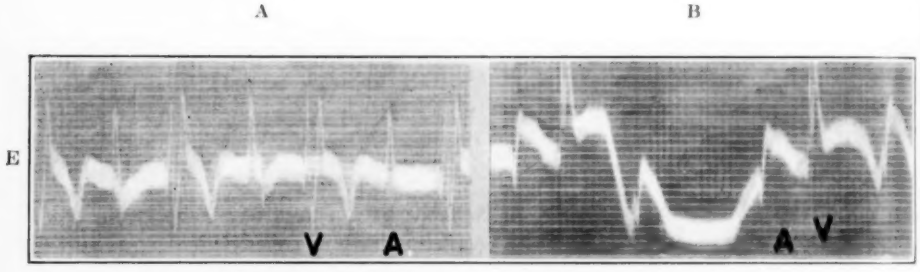

FIG. 4.—(*a*) Control, esophageal lead. (*b*) Development of auricular Q and elevation of auricular S–T resulting from localized necrosis of right auricle. Standardized 1.5 cm. = 10 millivolts.

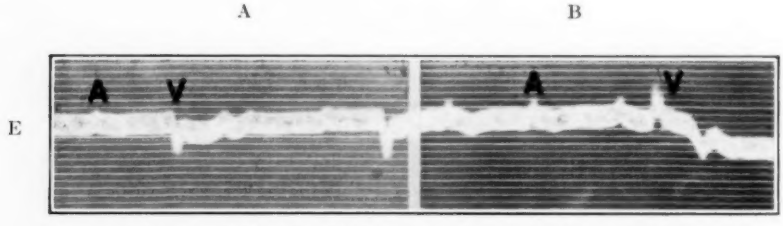

FIG. 5.—(*a*) Control, Lead I. (*b*) Inversion of auricular T_1, resulting soon after necrosis of left auricle. (Mechanical A–V block induced prior to control record.) Standardized 1 cm. = 10 millivolts.

A definite evolution of the auricular S–T changes was demonstrated in only 1 experiment in which an area of left auricular necrosis had been induced. The typical elevation of the auricular S–T_1 segment gave way to an inverted auricular T_1 followed by a restoration of the S–T segment, and a loss of the auricular Q_1 over a period of an hour. At the same time, deep auricular Q waves as well as an elevation of the auricular S–T segment and upright T_a wave were seen in the second, third and esophageal leads (Fig. 2, *a*, *b*, *c*). The ventricular complexes did not change in direction, the electrodes had not been altered, and the position of the heart did not appear changed during the period.

Non-specific changes occurred in the ventricular complexes in 11 instances. In 16 cases of definite localized auricular necrosis, electrocardiographic changes did not occur.

Discussion. The results of our experiments appear to substantiate the observations of other workers. The auricular S–T segment is usually obscured in clinical electrocardiograms by the ventricular complex and its actual deviation in impaired auricular coronary circulation cannot always be clearly observed without the use of the esophageal lead. The possibility that superimposition of an altered auricular S–T segment upon any portion of the succeeding ventricular complex may produce minor changes in the latter (see Fig. 2, *b*) must be considered. Occasional cases of so-called angina pectoris with slight changes in the ventricular complex or its S–T segment may actually be due to auricular infarction with changes in the auricular T and S–T segments which by superimposition lead to these variations.

In general, our criteria for localization of left auricular necrosis are similar to those of Abramson and his associates.[1] At times, however, instances of left auricular involvement produced auricular S–T elevation only in the third and esophageal leads. Further, in localization of right auricular involvement, we observed elevation of the auricular S–T segment in Leads II and III with marked changes of this type in the esophageal lead. Changes in Lead I usually consisted in diminished amplitude of the auricular QRS complex with little effect upon the S–T segment.

Our failure to observe changes in the auricular complexes in all cases of induced auricular necrosis is probably due to the presence of silent areas in the auricular appendages or possibly to the selection of superficial muscle bundles by the injected alcohol, to the exclusion of the deeper ones. Elevation of the auricular S–T segment in the second, third and esophageal leads appearing in some cases of left auricular necrosis may be dependent upon selective involvement of only part of the wall by the alcohol injected into the apparently similar area on different occasions. Such variations and the absence of changes on some occasions may possibly be explained by the work of Robb and Robb.[12a,b] Definite changes were noted in the esopha-

geal lead in some cases where they did not occur in the standard leads.

We believe that cases of angina pectoris or coronary thrombosis which give evidence of, 1, arrhythmias of auricular origin, 2, definite changes in the auricular complex, or, 3, only inconsiderable changes in the ventricular complexes, should be suspected of either impaired circulation to, or infarction of, the auricles. This may occur as the only lesion or in combination with ventricular involvement.

Summary. 1. The effect of localized auricular necrosis upon the electrocardiogram of the dog was studied, to help elucidate the changes in the auricular complex and minor changes in the ventricular complex occurring in coronary disease.

2. Necrosis near the sinus node resulted in a nodal rhythm, wandering pacemaker, auricular extrasystoles and paroxysmal auricular tachycardia.

3. Localized left auricular necrosis frequently produced elevation of the auricular S–T segment in Lead I with an upward bowing and an auricular Q wave. In 2 instances, intra-auricular block resulted.

4. In a few instances of left auricular necrosis, similar auricular S–T changes occurred in the esophageal lead, to the exclusion of Lead I.

5. Right auricular necrosis produced similar auricular S–T changes in the esophageal lead and in Leads II and III.

6. Changes in the initial auricular complex (P wave proper) consisted of broadening, inversion, diminution or increase in amplitude, and slurring, notching, the development of a Q or S wave, or M or W shapes.

7. Some cases of localized auricular necrosis failed to alter the electrocardiogram, while others produced minor changes in the ventricular complexes.

8. The similarity of such induced areas of localized auricular necrosis to clinically occurring auricular infarction was considered, and the possible clinical import of the results discussed.

I am indebted to Dr. L. N. Katz, under whose guidance this work was done, and to Dr. W. A. Brams for their interest and many helpful suggestions, and to Miss E Lindner and Mr. K. Jochim for invaluable technical assistance.

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METRAZOL CONVULSIVE SHOCK THERAPY IN AFFECTIVE PSYCHOSES.

A Follow-up Report of Results Obtained in Sixty-one Depressive and Nine Manic Cases.*

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In February, 1938, before the Missouri-Kansas Neuropsychiatric Association, I presented a preliminary report[1] of results obtained in 10 consecutive severe depressive psychoses by convulsive shock therapy. At that time I could find practically no reports in the literature indicating that the method had proved useful in other hands. I had overlooked a report of Wahlmann,[20] who, in 1936, stated that 1 manic depressive patient showing catatonic manifestations had obtained marked improvement after three shock injections. He concluded that the tendency to spontaneous remissions of this disorder argued against the specificity of the treatment.

Prior to publication of my report, Low *et al.*[13] reported on 16 patients with manic depressive psychoses—5 in the manic stage, 9 depressed, and 2 in the involutional period. In spite of the fact that the illness had lasted for more than 2 years in 6 of their patients, 5 got well. They concluded that in manic depressive psychoses treated with metrazol the rate of recovery does not depend upon the duration of the attack, as in schizophrenia. In comparing the treatment with prolonged narcosis, they felt shock therapy was definitely superior.

Since these reports, many others have confirmed the value of shock therapy in terminating severe depressive stuporous affective reactions. Verstraeten[19] reported favorable results in 3 depressed cases, but stated that manic patients react less favorably and he was disappointed in his results in schizophrenia. Goldstein, Dombrowski, *et al.*,[6] in a report on treatment of schizophrenia, included 1 depressed and 3 manic patients, but did not give specific results. Wyllie,[23] reporting from Scotland, treated psychoses other than schizophrenia. Two chronic depressed patients were much relieved and certain manic depressives, especially the stuporous cases, reacted very favorably, in his opinion. Kay,[12] treating 7 manic and 2 depressive patients, was able to relieve 3 manic states and the 2 depressed patients promptly. These results led him to feel that

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certain patients with affective psychoses react favorably and almost immediately to metrazol; that treatment of such patients is justified by material reduction of the duration of illness.

Mader[14] reported improvement in over 70% of 61 depressive patients, with one death in the series, which he did not attribute to treatment. He stated that many of his improved cases were practically cured, that very few depressives were uninfluenced by the treatment, and that long duration of illness did not affect prognosis as in schizophrenia. His best success was in the climacteric or involutional group, his poorest results with those showing profound anxiety or compulsive features. He concluded that the chief value of convulsive shock therapy in depressive states is to shorten the duration of illness.

Winn[21] reported 1 involutional depression of 2 years' duration with good recovery. Serko[17] reported 2 manic depressives with complete remission. Harris,[9] after treating 18 depressives of stupor type, reported complete recovery or improvement, even when evidence of deterioration seemed present. He recommends metrazol treatment for every case of stupor, regardless of duration; even if complete remission is not obtained, difficult psychiatric nursing problems such as forced feeding can be eliminated.

Cook[2] reported favorable results in 4 acute manic patients and 5 psychotic depressives. Of the latter, 1 relapsed to a slight degree, 1 became hypomanic. He was also impressed by results obtained with 3 hysterical patients, 1 ill for 12 years. He concluded that stuporous reactions are more favorably influenced because there are fewer dissociation phenomena than in schizophrenia. The abstraction from reality breaks down in the depressive reactions, and after the morbid affect clears, psychotic ideas and abnormal behavior evaporate.

Young and Young[24] in a recent article reported results obtained in 21 depressive patients, with improvement in all but 1. They likewise found best results in the chronic midlife stupor states. Read and others[16] reported a study of 49 manic depressives, 27 in manic phase, 13 depressives, 9 mixed. They concluded that metrazol is a valuable aid in treatment of functional psychoses.

As a result of my continued favorable experience with the use of convulsive shock therapy in both the depressive and manic phases I have followed up 70 patients: 61 depressive and 9 manic excitement states. The study of these patients over a period of time adequate to permit evaluation of results forms the basis of this report: particularly the permanency of recovery, the incidence of relapses, and refinements of therapy developed to prevent serious complications.

In my original report, I speculated on the psycho-physiologic reactions of shock therapy upon the emotional reactions of the individual. Since that time scientific evidence has accumulated to

give a more comprehensive theory as to the mechanism through which convulsive shocks improve the psychotic reactions. von Meduna and Friedman[15] attribute the benefits to stimulation or irritation of the whole central nervous system so extensive that mental barriers to certain thought processes are broken down, allowing these thought processes to be carried on properly. This seems very hypothetical and begs the point as far as explaining the reversal in feeling tone that is so characteristic of patients receiving this therapy. Gellhorn,[4] Gerard,[5] Himwich,[11] Hartman,[10] and others believe the fundamental influence of convulsive shock therapy, as well as of hypoglycemic shock, is through the production of cerebral anoxia: First, a deprivation of oxygen producing a powerful sympathetic stimulation; and secondarily, an opening up of cerebral capillaries, increasing oxygenation to the cerebral cells, thus enabling them to carry out their function more or less normally. Himwich[11] and Wortis[22] have shown during the marked period of apnea of the convulsive cycle that available oxygen for brain metabolism is markedly reduced.

Whether organic changes in the brain occur from repeated convulsive shocks is still unsettled. There is as yet no good experimental or necropsy evidence available to settle this point. Strecker[18] showed that repeated convulsions in rabbits produce capillary hemorrhages. A few experimental animals have shown other hemorrhagic tendencies. A few necropsy reports on humans have not confirmed this possible danger. However, clinically one notices that patients who have had a number of treatments complain of haziness of memory and relatives report that for some weeks following cessation of treatment patients show mild personality changes, amnesia, difficulty in recalling names, and so on, that suggest mild sensorium changes. There is some reason to believe the good therapeutic results occur from the organic changes produced by the confusional state induced by the convulsion. I have called attention elsewhere to the fact that the results obtained by shock therapy are strikingly similar to those reported from frontal lobotomy by Freeman.[3] He believes results occur because of organic brain changes producing a confusional state that breaks up obsessive thinking and thus patients are unable to worry.

Because of the possibility of producing permanent cerebral damage, especially in the involutional and presenile group, I have used as few shocks as possible and would rather run the risk of occasional relapses from insufficient treatment than slow up the intellectual functions of the patient or possibly produce permanent personality changes.

My experience with patients over 45 years of age still indicates that the method is quite safe in this age group. Repeated electrocardiographic studies on all patients past 55 years, some complicated by mild hypertension, some with actual coronary artery disease, have

as yet shown no apparent permanent cardiac defects from convulsive shock therapy. Dr. Willis D. Wright, who made the cardiac studies, has summarized the findings in this group as follows: Electrocardiograms were taken upon 40 depressed patients, aged 45 to 68 years. Of these, 34 patients had no clinical evidence of heart disease. The remaining 6 patients had definite heart disease, including 1 case of rheumatic heart disease with mitral stenosis showing no history of congestive failure; 1 congenital heart disease; 2 hypertensive heart disease; and 2 arteriosclerotic heart disease, 1 of these showing right bundle branch block. Five had suggestive but no conclusive evidence of coronary artery disease. In none of these patients was the original electrocardiographic pattern changed permanently by shock therapy. Repeated electrocardiographs following treatment demonstrated an abnormality in only 1 patient, an *A-V* block that persisted for 2 days.

In my original report, over one-third of the patients were past 55 years. We have had no complications arising from metrazol therapy in the older depressive group. In a few patients, treatment was discontinued temporarily because of intercurrent infections, but later resumed with good effect. My observation up to date does not conform to the absolute contraindications laid down by von Meduna and Friedman[15] in the use of this therapy.

The incidence of mechanical complications is undoubtedly higher than previously suspected and undoubtedly occurs more frequently than suspected. I have had 4 known fracture complications in about 1000 treatments, all in younger patients. Two were chronic schizophrenic patients and 2 had chronic depressions. Persistent back pains after shock therapy are probably the result of spinal fractures. Dr. W. R. Hamsa and myself[8] have recently reported upon traumatic complications from shock therapy, explaining the mechanism of production as comparable to fractures in tetanus and recommending preventive treatment. These complications are a serious drawback to the therapy and are one reason why its use should be restricted to serious psychotic states and to psychiatric hospitals in experienced hands. I consider metrazol therapy more hazardous than hypoglycemic shock.

As a routine procedure to prevent spinal and leg fractures, a spinal anesthetic of 10 mg. of pontocaine hydrochloride,* or 100 mg. of novocaine is given 1 hour before the metrazol injection. The anesthetic is dissolved in 4 cc. of spinal fluid obtained by a puncture between the first and second lumbar vertebræ by means of a 22-gauge needle and reinjected slowly intraspinally. This gives a transient anesthesia with complete sensory and motor paralysis of all the thoracic and lumbar segments. Since shock therapy is given every 3 days for about 5 to 8 injections in affective psychoses,

* We are indebted to the Winthrop Chemical Company for furnishing Pontocaine for investigative purposes.

the spinal anesthetic offers no serious drawback to treatment. At the onset of the tonic spasm both arms are held adducted against the chest. The greatest problem in complications is the possibility of fracture. Persistent backache should call for immediate radiologic examination.

In certain patients who are very apprehensive, we induce hypoglycemic shock first and at the onset of coma administer metrazol, immediately followed by intravenous hypertonic glucose. We have had no mechanical complications with this combined therapy. The tetanic spasm seems less severe after insulin shock has set in and this fact probably helps prevent fractures. In other patients fearful of the treatment, small doses of scopolamine, grains $\frac{1}{150}$ or $\frac{1}{100}$, given 1 hour before metrazol injection, are quite helpful in allaying anxiety and often make the patient totally amnesic to the individual treatment. We have found that many physicians inadvertently have frightened patients with potential danger of the therapy and have thus caused difficulty of treatment unless some such measure is adopted. We have not found that the use of scopolamine necessitates a larger dose of metrazol. We no longer use alkalinization, having become convinced the convulsive threshold is not lowered by its use.

Following the observation of Hall and Leibel[7] that experimental animals go into convulsions with one-half to one-fourth the usual dose of metrazol after the administration of adrenalin, we have frequently used adrenalin on patients apparently requiring large doses. By giving $\frac{1}{2}$ cc. of adrenalin intravenously, and at the moment of facial blanching, injecting metrazol, we have found that a good convulsive shock will result from half the usual dosage. This reduction we feel is an advantage because of less post-treatment nausea.

I am still inclined to repeat the initial injection plus 1 cc. immediately following the first injection if the patient has failed to have a convulsion. After a second failure I usually wait until the following day, unless the patient is very agitated or excited. We prolong the period of apnea by closure of the mouth and nose at the end of the convulsion for 30 to 60 seconds, as suggested by Freeman.

Although a good many psychiatrists recommend the therapy as applicable to home, office or general hospital management, I still disagree. Since the management of affective disorders is a difficult psychiatric procedure, it should, in my opinion, be administered only in well equipped psychiatric departments in the hands of experienced psychiatrists and psychiatric nurses. In several cases brought to my attention, patients in whom ambulatory treatment was attempted have refused further treatment and upon relapse their fears have driven them to suicide. It takes an unusual degree of rapport between doctor and patient to influence the patient to keep returning for repeated injections. Under strict psychiatric supervision these panic reactions are readily controlled and in no instance

have we had to discontinue treatment because of uncoöperativeness of the patient. Furthermore, while rapid termination of the affective disorder is the rule with shock therapy, efficient psychiatric nursing, psychotherapy, and other psychiatric treatment are very essential and can only be carried out in a closed department. We have also found that the interference of family, relatives and friends is a great deterrent to successful outcome, and thus no visit is permitted while the patient is under treatment. Disregard of these factors makes for poor results and increased frequency of relapses. We have found that it is advisable to hold the patient at least 2 weeks after the last shock, to be certain that the patient is ready to start social rehabilitation. The problem of personal situational factors on the patient's return to his previous environment is of extreme importance and requires prolonged follow-up educational psychotherapy of the family and associates, in order to increase the permanency of the results.

In Table 1, the results obtained in both the depressive and manic patients treated up to date are evaluated.

TABLE 1.—RESULTS OBTAINED IN AFFECTIVE DISORDERS BY CONVULSIVE SHOCK THERAPY. (70 CASES—61 DEPRESSIVE AND 9 MANIC STATES.)

Diagnosis.	No. of cases. Sex.	Age.	Duration of psychosis.	Average shocks.	Days under treatment.	Time followed.	Result.*	Relapse.
Reactive depression	16 11 F 5 M	27–67	2 mos.–1½ yrs.	6.5	23	3 over 1½ yrs. 1 over 1 yr. 5 over 6 mos. 7, 3 mos.	9 A 7 B	2 (1 suicide)
Manic depressive: depressed	21 9 F 12 M	29–65	1 wk.–6 yrs.	5.7	18	4 over 1½ yrs. 6 over 1 yr. 3 over 6 mos. 8, 3 mos.	10 A 11 B	3 (1 recovered second course)
Involutional melancholia	24 14 F 10 M	42–68	1 wk.–3 yrs.	6.5	21	3 over 1½ yrs. 9 over 1 yr. 4 over 6 mos. 8, 3 mos.	11 A 12 B 1 C	4 (2 recovered second course)
Manic states	9 7 F 2 M	26–53	1 wk.–9 mos.	4	16½	1 over 1½ yrs. 3 over 1 yr. 3 over 6 mos. 1, 3 mos.	4 A 4 B 1 C (died)	2 (1 recovered second course)

* Result: A = Complete remission with full insight; return to former social level.
B = Social remission, able to adjust at home but with some residual symptoms, usually anxiety. Incomplete insight.
C = Unimproved; relapses all occurred in B group.

Summary of Treatment Results. Of 61 depressed patients, 28 (45%) have obtained a full remission lasting from 3 to 18 months; 32 (52%) obtained a social recovery; but 7 (11%) relapsed. Four of these were improved again with a second course of treatment; 1 remained unimproved, and 1 committed suicide. Fifty-seven (90%) of the 61 patients, obtained rapid improvement with termination of the depression by metrazol shock therapy. Over 50% of these patients were past 45 years and 42% were past 55; the oldest

was 68. Four of these patients were chronic state hospital patients of from 1 to 6 years' duration.

Four (44%) of 9 manic states obtained a full remission lasting from 3 to 18 months; 4 (44%) obtained a social remission, but 2 relapsed, 1 recovering subsequently and 1 dying of intercurrent infection while under treatment.

The average number of shocks given every 2 to 3 days for the depressives was 6 to 7, with an average period of 3 weeks under treatment; the average number of treatments for the manics was 4, the average duration 16½ days. One case of depression of 6 years' duration gave a classical depressive history, but exhibited the behavior of a catatonic with continuous stupor for 6 years.

Conclusions. 1. Convulsive shock therapy, in spite of certain hazards, is an indicated therapy in chronic depressive and manic affective states.

2. Ninety per cent of severe depressive reactions are terminated within 2 to 3 weeks' treatment.

3. Therapy is most effective in the midlife and presenile depressions. It has proved to be a safe procedure in the older group.

4. Two-thirds of the severe manic states can likewise be terminated by convulsive shock therapy.

5. Convulsive shock therapy should only be given in well equipped psychiatric departments.

6. Spinal and lower extremity fractures are common complications. These can be prevented by administration of a spinal anesthetic prior to shock therapy.

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METABOLIC AND CARDIOVASCULAR EFFECTS OF INTRAMUSCULAR INJECTIONS OF ADRENALIN AND OF AMPHETAMINE.

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The reports that fatigue is influenced by adrenalin[7] and amphetamine[8] have led us to compare the effects of these sympathomimetic drugs on the utilization of carbohydrate, the concentration of sugar and lactic acid in blood and of acetone bodies in blood and urine, the oxygen consumption, the acid-base balance, the pulse and the blood pressure. Four normal fasting men were studied over 4-hour periods while reclining quietly on a bed.

In one series of experiments no drug was administered; 2 subjects who were unacquainted with the plan received intramuscular injections of physiologic saline. After an initial rest of 30 minutes, capillary blood was collected at 15-minute intervals for sugar and lactic acid determinations. At less frequent intervals, venous or arterial blood was drawn for acid-base studies. The subject was connected with an open circuit metabolism apparatus and expired air was collected continuously for $3\frac{1}{2}$ hours, allowing 1 minute every $\frac{1}{4}$ hour for drawing samples and emptying the gasometer. Pulse and blood pressure were observed frequently.

In other experiments, the drug was injected intramuscularly after preliminary observations lasting about 1 hour. One milligram of adrenalin chloride (Parke Davis & Co.) in 0.1% solution or 20 mg. of amphetamine sulphate (Smith, Kline and French Lab.) in 2% solution was used. In some instances, arterial blood was drawn for gas analysis just before injection of the drug and again at the conclusion of the experiment. At least a week elapsed between experiments on a given subject.

Carbohydrate Utilization. The estimation of the utilization of carbohydrate is complicated when the accumulation of a fixed acid such as lactic displaces carbon dioxide from body reserves of bicarbonate. It is on this account that observed increases in the R.Q. shortly after injecting adrenalin have not been accepted as evidence for greater utilization of carbohydrate. Analyses by Cori and Cori[2] of liver and muscle in rats gave the first proof that adrenalin may,

but does not necessarily, lead to an increase in oxidation of carbohydrate. It mobilizes muscle glycogen "*and it depends on the metbolic state of the animal (presumably on the insulin content of the tissues) to what extent the glycogen mobilized in the muscles is being oxidized.*" We emphasize this conclusion because some have the impression that adrenalin effects a reduction in carbohydrate oxidation. For example, it has been suggested by Himwich and Fulton[5] that fat is the fuel of emotion, and Cameron[1] has been criticized in his discussion of adrenalin hyperglycemia for not taking into account preferential burning of fat. The principle of our procedure is the same as that employed a few years ago[4] in an investigation of adrenalin effects on energy exchange in exercise: the measurements were made over the entire period of formation and removal of excess lactic acid.

Sufficient time was allowed for completing the cycle of lactic acid formation and removal (Fig. 1). The final values for blood lactate ranged from 8.9 to 14.7 mg. %, averaging 12 in the control experiments, and from 10 to 17.8, averaging 12.8, about 2½ hours after adrenalin injection. There is no evidence of any effect of amphetamine on blood lactate under the experimental conditions.

The corresponding curves for blood sugar in Figure 2 show the same general trend: recovery was complete 2½ hours after adrenalin and a constant level was maintained in the control and the amphetamine experiments.

The possibility that other acids than lactic may have accumulated to a sufficient extent to modify acid-base balance was tested by measurement of CO_2 combining capacity of oxygenated blood at pCO_2 40. Notable decreases occurred following adrenalin but after 2½ hours the original value was restored. The changes observed were approximately equivalent to the increases in lactate concentration, indicating that no other fixed acid was present in quantitatively significant amounts. There were no consistent changes in alkaline reserve following amphetamine injection.

The only other possibility that needs to be considered is that the drugs may have upset respiratory regulation enough to modify the pH and CO_2 content of arterial blood. Arterial blood was drawn from 2 subjects before and 2½ hours after drug administration. There was an average decrease of about 1 vol. % after adrenalin and about 2 vol. % after amphetamine. If we assume that body fluids underwent a net loss of 1.5 vol. % of CO_2 during the 2½ hours the total net loss was about 1 liter and the ratio of net loss to total production about 1 in 35. The R.Q., consequently, would be greater by about 0.02 than the R.Q. of the oxidative processes. It is by no means certain that changes in arterial blood reflect accurately changes in tissue fluids since their CO_2 content depends on the rate of blood flow and the oxygen utilization, as well as on composition of arterial blood. It is safe to say, however, that

2½ hours after injecting these drugs respiratory regulation was virtually normal in the case of adrenalin and only slightly affected in the case of amphetamine. In summary of the foregoing considerations, it appears that the R.Q. as measured over the entire period may have been slightly high in the case of amphetamine and was a fair measure of the proportion of carbohydrate utilized in the case of adrenalin.

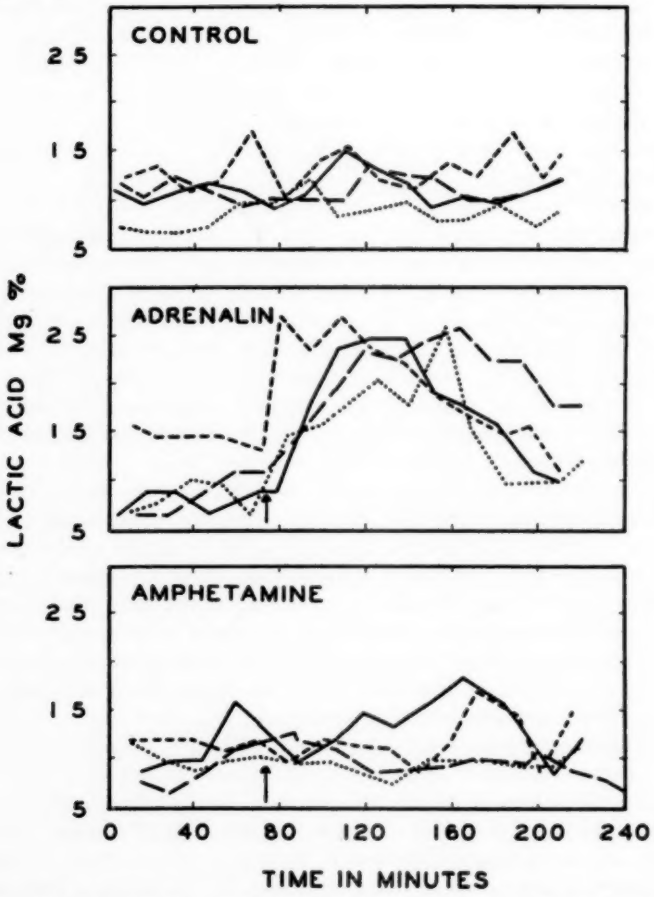

FIG. 1.—Blood lactate in control experiments and before and after intramuscular injection of 1 mg. of adrenalin or 20 mg. of amphetamine.

The R.Q. changes in the 4 individuals are shown in Figure 3. Only after adrenalin is there much deviation from the horizontal trend. The course is roughly parallel to the changes in lactic acid concentration. When lactic acid is accumulating, the R.Q. is higher than corresponds to oxidative processes, but if its rise is

solely dependent on displacement of CO_2 from reserves in tissue fluids there should be a correspondingly low level when lactic acid is being removed and CO_2 is being retained. An inspection of the curves does not indicate a drop in R.Q. values below the base line. With a single exception, the mean increments in R.Q. for each period after adrenalin for the 4 men are all positive; the mean

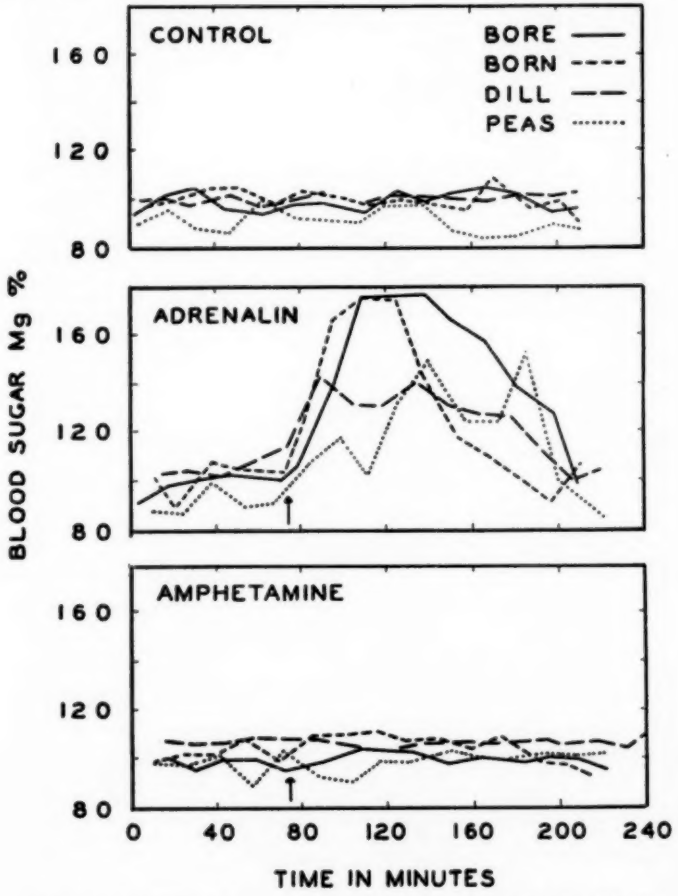

FIG. 2.—Blood sugar before and after adrenalin or amphetamine injection.

increment for the 40 postinjection periods is +0.043. It seems reasonable to conclude that the injection of adrenalin did not reduce utilization of carbohydrate in the body as a whole, but probably slightly increased it.

The appearance of acetone bodies in blood and urine is generally accepted as evidence of faulty utilization of carbohydrate. The report of Hubbard and Wright[6] that acetone bodies in human blood

may increase from resting levels of from 0.2 to 0.7 mg. % up to 0.4 to 2 mg. % after injecting 1 mg. of adrenalin has been advanced as evidence that the adrenalin reduces utilization of carbohydrate.

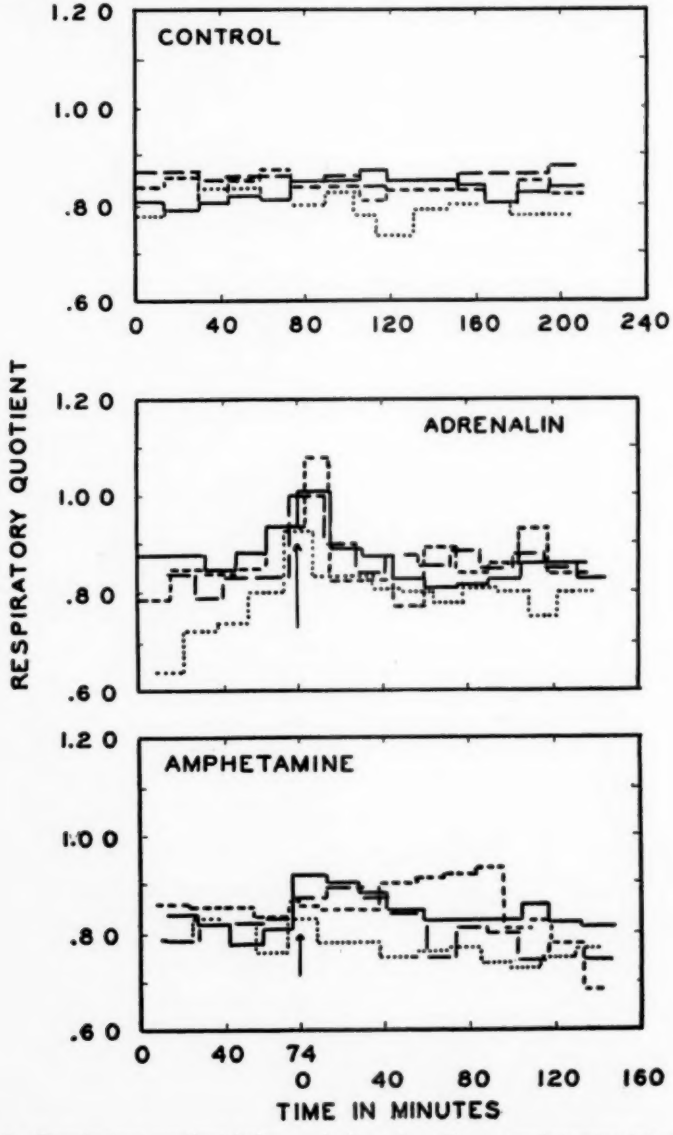

FIG. 3.—Respiratory quotient before and after adrenalin or amphetamine injection.

Determinations of total acetone bodies in blood and urine by Van-Slyke's method[10] are summarized in Table 1. The changes after

adrenalin were like those observed by Hubbard and Wright and the return to the original level (or below it in 2 cases) also was noted. Acetone bodies increased in 3 of the 4 subjects after amphetamine. However, as great an increase occurred in the control experiments as after either drug. None of these changes are important quantitatively and we are not disposed to attach much significance to them. On the basis of the analyses of blood alone we are of the opinion that adrenalin was not responsible for an increase in acetone bodies and may have delayed the onset of ketosis that normally occurs 18 to 24 hours following the last meal. This suggestion is supported by the analyses of urine. All subjects exhibited a slight ketonuria in the control observations while none did so after adrenalin.

TABLE 1.—ACETONE BODIES.

(All concentrations are in mg. per 100 cc. Zero time corresponds to beginning of first metabolism period.)

	Blood.				Urine acetone.	Urine vol., cc.
Mean time of samples, minutes	66	96	125	213	220	220
Control:						
Borel	0.2	0.2	0.4	...	0.5	472
Bornstein	0.1	0.4	0.9	...	4.8	185
Dill	1.1	2.1	2.0	...	0.3	432
Pease	0.2	0.6	1.0	...	8.9	306
1 mg. adrenalin at 74 minutes:						
Borel	0.4	0.1	0.0	0.2	0.0	855
Bornstein	0.2	0.6	0.4	0.2	0.0	
Dill	0.2	0.6	0.2	0.2	0.0	460
Pease	0.5	1.0	0.7	0.2	0.0	
20 mg. amphetamine at 74 min.:						
Borel	0.2	0.4	0.7	0.9	0.0	
Bornstein	0.1	0.2	0.7	0.0	0.0	400
Dill	0.0	0.7	0.1	0.6	0.0	
Pease	0.7	0.2	0.0	0.7	6.0	292

Oxygen Consumption. The calorigenic effect of adrenalin is well established, but there have been conflicting reports regarding the oxygen consumption after amphetamine administration. The graphic records of our experiments in Figure 4 show quite clearly that there was a sharp increase in metabolic rate after adrenalin with a return to the level of control experiments after 2½ hours, while after amphetamine the rise was less abrupt but more sustained. The mean increments in oxygen consumption in Periods 5 to 14 over the mean value for Periods 1 to 4 averaged 7.7 cc. per minute in the control experiments, 39 after adrenalin and 25.1 after amphetamine. The increments during the last ½ hour were, in the same order, 12, 12 and 30. This is good evidence for the more sustained nature of the calorigenic influence of amphetamine. A quantitative measure of the calorigenic effect of these drugs must take into account the tendency of metabolism to rise in the control experiments, possibly because of restlessness. It was greater, on the average, by 3% during the last 10 periods than during the first

4 periods. Assuming that the same influences were operative during the drug experiments, we are left with an increase, during the 2½ hours following injection, of 13% after adrenalin and 7% after amphetamine. It is possible that these increases in metabolic rate

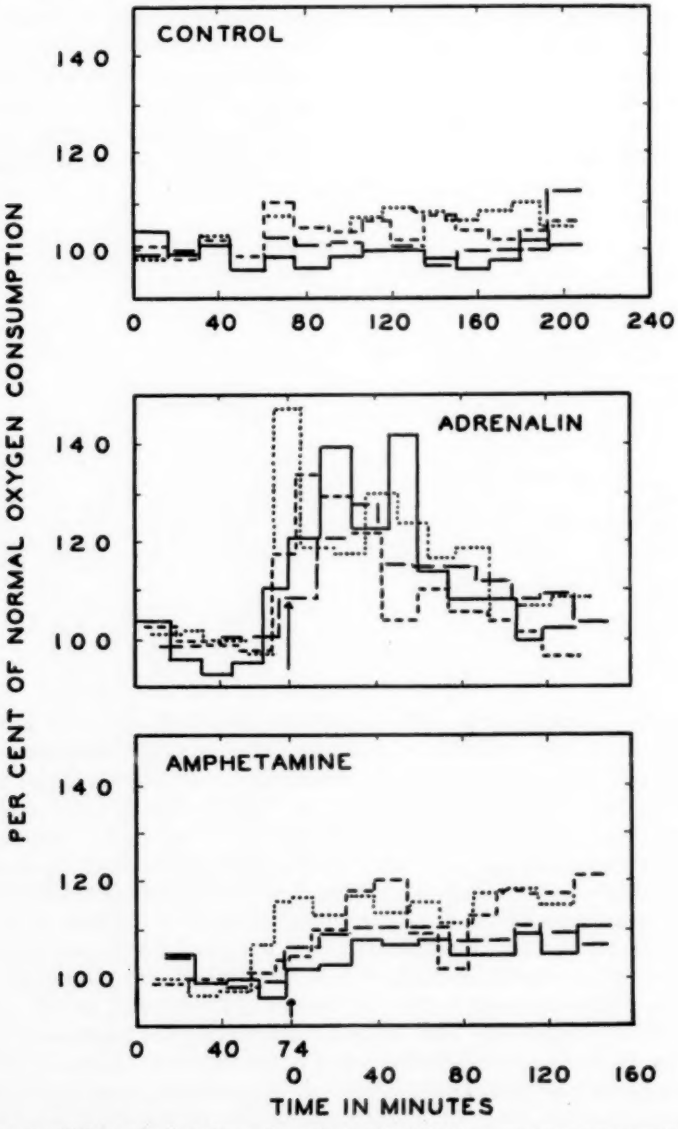

FIG. 4.—Effects of adrenalin and amphetamine injections on oxygen consumption. The normal value is taken as the mean oxygen consumption over a period of about 1 hour before administering the drug.

depend in part on greater restlessness rather than entirely on intrinsic calorigenesis but of this we have no measure.

Respiratory Regulation. The facts already presented regarding arterial blood have a direct bearing on respiratory regulation. There was the well-known tendency to overventilate while lactic acid concentration was rising after adrenalin, and when the original concentration was restored the CO_2 content of arterial blood closely approached its original level. At the same time the respiratory rate either increased slightly or remained constant. After amphetamine the respiratory rate remained constant, but there was a slight tendency to overventilate as shown by the lower concentration of CO_2 in arterial blood, already referred to, and a lower percentage of CO_2 in expired air.

Pulse and Blood Pressure. The transient effect of adrenalin on metabolism was accompanied by considerable increases in pulse rate (Fig. 5) and in systolic blood pressure, and by a significant decrease in diastolic blood pressure (Fig. 6). Amphetamine, on the other hand, produced little effect on pulse rate (in 1 man there was a decrease and in another an increase) but a large and sustained effect on systolic blood pressure. Just as the metabolism had reached its highest level in the last hour, so the systolic pressure tended to rise and in 2 subjects was highest at the end. The diastolic pressure also increased somewhat in 3 men and very considerably in the fourth. While both drugs raised the systolic blood pressure the mechanisms probably are different since the heart rate is increased in the 1 case and virtually unchanged in the other.

Discussion. Experiments such as ours have effects that depend on rate of absorption and rate of destruction of the drug. There is also the possibility of increased liberation of antagonistic substances—such as insulin. From the pharmacologic point of view, more easily interpretable results might be obtained by perfusion of isolated organs, but under many circumstances physiologic action can best be judged by observations of the intact and non-anesthetized animal. In interpreting our experiments we cannot deduce simple cause and effect relations, but it is possible to evaluate the resultant of the interplay of forces set in action by injection of these drugs.

The disagreement regarding the effects of adrenalin on utilization of carbohydrate is a consequence of inadequate data. In the early stages of the argument it was assumed that since blood sugar increased, utilization of carbohydrate increased. Later it was shown that the R.Q. increases but this was attributed to displacement of CO_2 by lactic acid. The antagonistic relation between adrenalin and insulin and the report of Hubbard and Wright[6] that acetone bodies in the blood increase after adrenalin injection gave support to the opinion expressed by Peters and Van Slyke[9] that adrenalin interferes with carbohydrate utilization. There is no basis for such

a conclusion in the work of Cori and Cori,[2] and our experiments in exercise[4] demonstrating increased utilization of carbohydrate do not conflict with their observations. The present experiments on resting subjects in the postabsorptive state show a much smaller

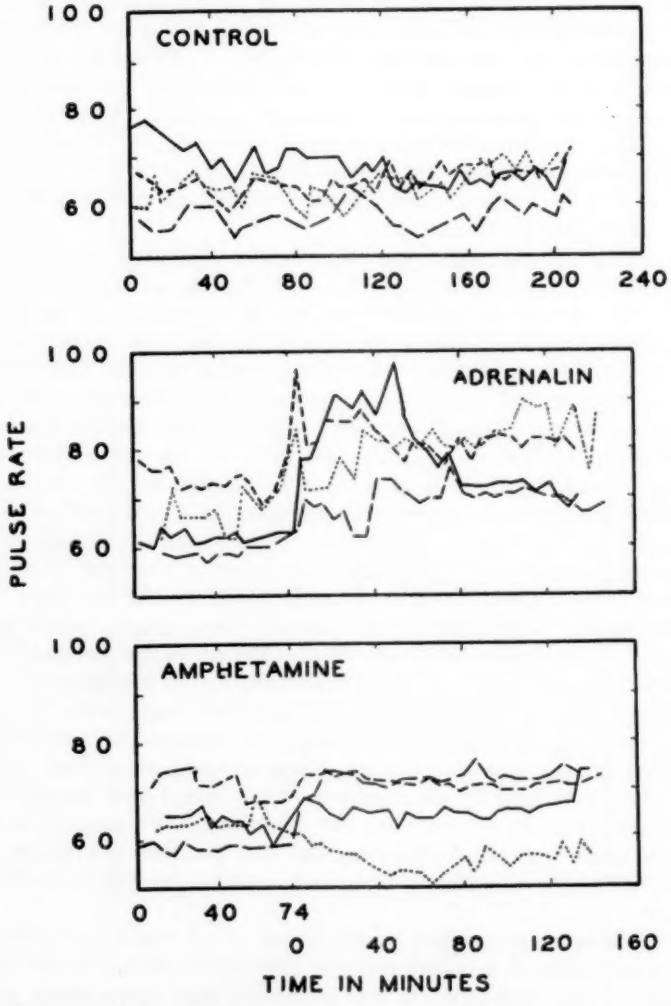

FIG. 5.—Pulse rate before and after adrenalin or amphetamine injection.

rise in R.Q. than in exercising subjects: this observation is in agreement with Cori's conclusion that the proportion of mobilized glycogen oxidized depends on the metabolic state of the organism. If our resting subjects had had smaller reserves of carbohydrate, there might have been no change or even a reduction in its oxidation,

BLOOD PRESSURE IN MM Hg

as seen by Cori in rats that had fasted for 24 hours. This is suggested by the results of some preliminary experiments on subjects who had been 24 hours without food. Injection of adrenalin under

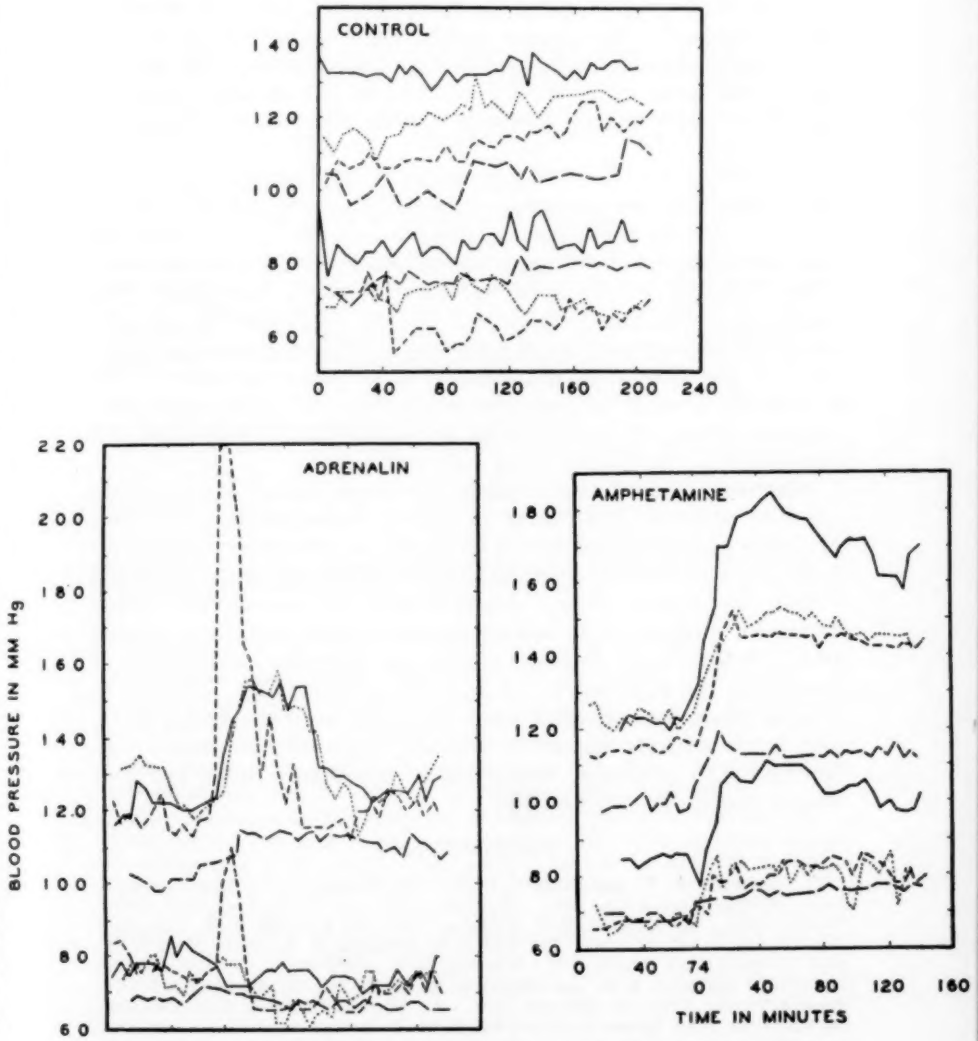

FIG. 6.—Systolic and diastolic blood pressure before and after adrenalin or amphetamine injections.

such circumstances produces an unmistakable rise in urinary acetone, in contrast with the experiments reported here on subjects who had been without food for from 12 to 16 hours.

We agree with the conclusion of Courtice, Douglas, and Priestley[3] that in fasting subjects at rest there is little effect of adrenalin injections on the proportion of carbohydrate utilized. In 1 of their subjects, the mean R.Q. during 150 minutes following the subcutaneous injection of 0.5 mg. of adrenalin decreased 0.02 and in a second it was unchanged. We cannot accept their deduction from such experiments that adrenalin does not increase carbohydrate utilization in exercising subjects. In our opinion, the affirmative experimental evidence of Dill, Edwards, and de Meio[4] on this subject is conclusive.

The qualitative effects of adrenalin and amphetamine are no less interesting than the quantitative variation among normal individuals. According to preliminary observations the types of response seen, particularly in blood sugar and in blood pressure after adrenalin (Figs. 2 and 6), are apt to be characteristic of the individual. The significance of this phenomenon can only be determined by repeated observations on a number of subjects of different emotional types. There is the prospect of obtaining by such tests an objective index to the effectiveness of hormonal regulation and of the autonomic nervous system, at least in so far as carbohydrate metabolism and cardiovascular mechanisms are concerned.

Summary. Intramuscular injections of adrenalin in normal fasting men either did not change or slightly increased the proportion of carbohydrate utilized during the period in which blood sugar and lactate were elevated. Acetone bodies in blood and urine fluctuated within the normal range. Amphetamine did not modify carbohydrate utilization or the concentrations of sugar, lactate or acetone bodies in the blood. It had a calorigenic effect that was smaller in magnitude but more sustained than that of adrenalin. The rise in systolic blood pressure after amphetamine was greater in 1 subject, and in all subjects was more sustained than after adrenalin. In contrast with adrenalin, amphetamine produced a small but consistent rise in diastolic pressure.

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BOOK REVIEWS AND NOTICES

THE CLINICAL AND EXPERIMENTAL USE OF SULFANILAMIDE, SULFAPYRIDINE AND ALLIED COMPOUNDS. By PERRIN H. LONG, M.D., Associate Professor of Medicine, The School of Medicine, The Johns Hopkins University; Associate Physician, The Johns Hopkins Hospital, etc., and ELEANOR A. BLISS, Sc.D., Fellow in Medicine, The School of Medicine, The Johns Hopkins University. Pp. 319. New York: The Macmillan Company, 1939. Price, $3.50.

IN this monograph on sulfanilamide and sulfapyridine and allied compounds the authors have thoroughly reviewed the literature up to 1939. Laboratory workers will find complete bibliographies pertaining to the chemotherapy of experimental bacterial infections and experimental toxicity and comparative pharmacology of sulfanilamide and allied compounds. The section on the mode of action of sulfanilamide is well summarized on page 141, "So far, then, no theory has been evolved which adequately explains the mode of action of these sulfur benzene derivatives . . . . The speculations of Levaditi, Lockwood, and Mellon . . . should prove a stimulus to other workers."

Every practicing physician would profit by reading the chapters dealing with the clinical use and the clinical toxic manifestations of sulfanilamide. Unfortunately, at the time of writing, the authors had had little experience with sulfapyridine, and the 11 pages devoted to the clinical use of it serve only as an introduction to this new sulfanilamide derivative. Drs. Long and Bliss are to be commended on this accurate presentation of such a complex and ever-increasing phase of chemotherapy. H. F.

MENSTRUAL DISORDERS. Pathology, Diagnosis and Treatment. By C. FREDERIC FLUHMANN, B.A., M.D., C. M., Associate Professor of Obstetrics and Gynecology, Stanford University School of Medicine, San Francisco; Assistant Visiting Obstetrician and Gynecologist to Lane and Stanford University Hospitals, etc. Pp. 329; 119 illustrations. Philadelphia: W. B. Saunders Company, 1939. Price, $5.00.

DR. FLUHMANN'S clinical experience has been combined with the essence of his scientific research to produce a most welcome volume on the subject of "Menstrual Disorders." The subject matter is divided in logical sequence into 19 chapters which cover all the phases of the subject.

The first 5 chapters discuss the history, and physiologic and anatomic changes of the reproductive organs during the menstrual cycle, while a chapter on the comparative physiology of menstruation explains biologic differences in various mammals. Of particular value is a chapter on modern methods of investigation in which Dr. Fluhmann discusses the methods of analysis used to determine the content of the different hormonal elements in various body fluids. He also discusses and clarifies the significance of the results and the relative unit values of such tests. He is conservative in his statements as to therapeutic value of various hormones. In this connection he lists the commercial preparations now available, and also discusses the subject of irradiation of the ovaries and hypophysis. The latter part of the book takes up etiology, pathology, and treatment from a general standpoint, as well as by hormones. The book closes with an excel-

lent presentation of the modern conception of the menopause, and the methods of alleviating the often troublesome symptoms.

The author has been conservative in his suggestions for treatment in the various diseased conditions discussed, realizing, undoubtedly, the truth of his statement he makes in Chapter 8: "Most menstrual disorders are not primary diseases, but are secondary developments from systemic and pelvic condition." The book is highly recommended to the entire profession, for there are few physicians who do not come in contact with some expression of menstrual disorders in their daily practice. P. W.

PROBLEMS OF AGEING. Biological and Medical Aspects. A publication of the Josiah Macy Jr. Foundation. Edited by E. V. COWDRY, Washington University, St. Louis. Twenty-six Contributors. Pp. 758; 120 illustrations, many tables. Baltimore: The Williams & Wilkins Company, 1939. Price, $10.00.

THIS book is composed of 25 chapters by as many different authors who cover a range in their respective fields broad enough to include botany, anthropology, geriatrics and in particular the ageing process as seen in each system of the body individually. The importance of the study from a broad human aspect is self evident. From the point of view of the medical profession in this day of diminishing childhood mortality, the consideration of this process and in particular the early changes indicative of age becomes the basis of the preventive medicine of the later decades. So sharp a focus as the title implies when dealt with by so many authors has of necessity led to some overlapping of the material. This has proved in the main an advantage, however, for the subject when it ceases to be purely descriptive becomes at once rather speculative and hence a contrast of points of view is advantageous. On the other hand, one is at times impressed with the possibility that an author is trying too carefully to stay within his field and thereby contracting an expression of opinion that would be better if expanded. For the practitioner of medicine the book holds a supply of factual tabulated data that is easily accessible and is as essential to a consideration of the ageing patient as standard tables of height and weight are for those dealing with children. W. A.

MOLDING AND CASTING. Its Technic and Application for Moulage Workers, Sculptors, Artists, Physicians, Dentists, Criminologists, Craftsmen, Pattern Makers and Architectural Modelers. By CARL DAME CLARKE, Associate Professor of Art as Applied to Medicine, University of Maryland School of Medicine. Pp. 308; 69 illustrations. Baltimore: The John D. Lucas Company, 1938. Price, $4.50.

A MOST valuable working compend for those employing the plasters and waxes in impression and reproduction work. This book is of particular value for the many formulæ given and the details of technique. It is strongly recommended as an authoritative reference book. G. W.

OH, DOCTOR! MY FEET! By DUDLEY J. MORTON, Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University. Pp. 116; 3 illustrations and 6 plates. New York: D. Appleton-Century Company, 1939. Price, $1.50.

THE author of that splendid work "The Human Foot" has tried to popularize foot care. This attempt suffers from a somewhat lumbering and weighty humor. G. W.

THE MARCH OF MEDICINE. Selected Addresses and Articles on Medical Topics, 1913–1937. By RAY LYMAN WILBUR, M.D., President of Stanford University. Pp. 280. Stanford University, Calif.: Stanford University Press, 1938. Price, $2.75.

DURING his distinguished career as physician, teacher, administrator and cabinet officer, the author has had many calls to bring messages of counsel and inspiration, based on his rich and varied experience, to many groups, lay and medical. In this volume have been gathered thirty addresses, some reprinted from journals and society proceedings, some appearing in print for the first time, delivered over a span of 25 years. Dealing with various phases of medical teaching, postgraduate education, public health and medical economics, they give a remarkable survey of the progress and the problems of medicine and the medical profession that well merits the title, taken from that of the closing article, The March of Medicine. All physicians and medical students will find here much that interests and that challenges to thought and action. R. K.

SURGICAL APPLIED ANATOMY. By SIR FREDERICK TREVES, BART. Pp. 748; 192 illustrations (66 in color). Tenth edition, revised by LAMBERT ROGERS, M.Sc., F.R.C.S., F.R.C.S.E., F.R.A.C.S., F.A.C.S., Professor of Surgery, University of Wales; Honorary Surgeon and Director of the Surgical Unit, Cardiff Royal Infirmary, etc. Revised from the ninth edition, prepared by the late PROFESSOR C. C. CHOYCE, C.M.G., C.B.E., M.D., F.R.C.S. Philadelphia: Lea & Febiger, 1939. Price, $4.50.

This Applied Anatomy seems to require a new edition almost every year or so. The same format has been maintained as was present in the other editions. In this edition the sections on the eye, ear, nose and throat have been modernized and new sections and illustrations have been added throughout the book. It should still maintain its position as a readily accessible, anatomic reference manual and should appeal to students of anatomy and surgery because of its small size, its excellent subject material and its relatively low cost. L. F.

CANCER OF THE COLON AND RECTUM. Its Diagnosis and Treatment. By FRED W. RANKIN, B.A., M.A., M.D., Sc.D., F.A.C.S., Surgeon, St. Joseph's and Good Samaritan Hospitals, Lexington, Ky., and A. STEPHENS GRAHAM, M.D., M.S. (in Surgery), F.A.C.S., Surgeon, Stuart Circle Hospital, Richmond, Va.; Assistant Professor of Surgery, Medical College of Virginia. Pp. 358; 133 illustrations and 54 tables. Springfield, Ill.: Charles C Thomas, 1939. Price, $5.50.

THE authors state that their purpose is to present the progress in the diagnosis and practical offensive maneuvers against cancer of the large bowel, one of the outstanding surgical accomplishments of the past quarter century. They offer not only their own experience, which has been wide, but also that of other authors.

The first section, general considerations, thoroughly discusses the anatomy and physiology of the large bowel, the incidence and etiology of its cancer and its pathology, symptoms and differential diagnosis. The section on anatomy and physiology includes frequent surgical considerations. The authors give their opinion that most of the lesions of the large bowel begin as adenomatous polyps, which are discussed in detail. They consider the various grades of tumor (Broders) and show illustrative microphotographs.

Part II, on diagnosis and treatment, discusses such subjects as operability and prognosis, choice of operation, radiotherapy, operative mortality and end-results, pre- and postoperative treatment. The authors support the view that a colostomy is necessary in most cancerous lesions of the colon and rectum, in order to perform a sufficiently radical operation. They do not condemn resection with primary anastomosis; but believe that the old dictum that "the smaller and the earlier the growth the better the chance of cure and the more extensive the operation should be" still holds good today. In this section are also described the various operations for cancer in the various portions of the large intestines, giving indications for their use.

In the chapter on radiotherapy of carcinoma of the rectum, which he regards as a "surgical disease," Dr. F. M. Hodges limits radiotherapy to the treatment of inoperable cases or cases in which operation is refused. He uses both external radiation and the implantation of radium seeds.

The chapter on operative mortality and end-results contains a review of the published statistics of practically all the large clinics. The statistics are hardly comparable because of differences in classification but nevertheless will be useful for those interested.

An excellent chapter on the authors' technique and pre- and postoperative treatment is especially valuable for the detailed description of the routine which they have successfully used.

The last part of the book, on operative treatment, describes and illustrates the various procedures in detail. The final section discusses palliative and various miscellaneous procedures of value in connection with the treatment of carcinoma; they mention colocolostomy, resection of the presacral nerves and so forth. The book is relatively small but so well written and so nicely condensed as to be thorough in every detail. It is one which can hardly be omitted from the library of a medical man or surgeon who is interested in lesions of the large intestines. L. F.

MEDICINE IN THE OUTPATIENT DEPARTMENT. An Introductory Handbook. By WINTHROP WETHERBEE, JR., M.D., Junior Visiting Physician, Boston City Hospital. With a Foreword by GEORGE R. MINOT, M.D., S.D., F.R.C.P. (EDIN. and LOND.), F.A.C.P., Professor of Medicine, Harvard University; Director, Thorndyke Memorial Laboratory; Visiting Physician, Boston City Hospital. Pp. 111. New York: Paul B. Hoeber, Inc., 1938. Price, $1.00.

SOME excellent advice for the guidance of the medical student's first clinical steps in the outpatient department; concise, to the point, and conveniently encompassed in a pocket-size booklet. As Dr. Minot says in his foreword, "Every paragraph might be expanded to a long chapter, but the value of the contribution lies in the clear, brief, and fundamental statements with which every medical student should not only be familiar, but which he should never neglect to utilize." R. K.

A TEXTBOOK OF PHYSIOLOGY. By WILLIAM D. ZOETHOUT, PH.D., Professor of Physiology in the Chicago College of Dental Surgery (Loyola University). Pp. 714; 291 illustrations. Sixth edition. St. Louis: The C. V. Mosby Company, 1938. Price, $4.00.

THIS admirable text is now issued in its sixth edition. Much new material has been added so that it is thoroughly up to date. The illustrations are selected so as to be coördinated with the text. It is a book well adapted for use in the instruction of dental students. B. McG.

TREATMENT BY DIET. By CLIFFORD J. BARBORKA, B.S., M.S., M.D., D.Sc., F.A.C.P., Department of Medicine, Northwestern University Medical School, Chicago, etc. Pp. 691; 1 illustration. Philadelphia: J. B. Lippincott Company, 1939. Price, $5.00.

THAT a fourth edition has appeared since the first in 1934 proves that the book has achieved its purpose as a "simple, crystallized, practical and workable method of prescribing diets" in health and disease. New material includes chapters on Addison's disease and chronic hyperinsulinism, also extensive revision of the section on vitamins, and others. R. K.

OPERATIVE ORTHOPAEDICS. By WILLIS C. CAMPBELL, M.D., Memphis, Tenn. Pp. 1154; 845 illustrations. St. Louis: The C. V. Mosby Company, 1939. Price, $12.50.

THIS book is a most important addition to surgical literature and an efficient supplement to recent books on orthopedics. It describes in detail with accompanying illustrations the current bone and joint operative procedures. These are chronologically arranged according to Surgery of Joints, Bone, Muscles, Tendons, Nerves, Static Affections and Congenital Deformities. The subject of Joints, for example, deals separately with the surgical procedures used in acute infectious arthritis, low-grade affections of joints, arthrodesis, ankylosis and deformity, arthroplasty, traumatic lesions of joints and dislocations. There are over 200 pages devoted to Fracture Surgery, covering acute, malunited, delayed and ununited fractures. The introductory chapters greatly enhance the clear presentation of the material by describing the author's method of estimating joint motion, the present concept of bone physiology and pathology, surgical technique, orthopedic instruments and apparatus, and surgical approaches to bones and joints. J. N.

MEDICAL MICROBIOLOGY. By KENNETH L. BURDON, PH.B., SC.M., PH.D., Assistant Professor of Immunology and Bacteriology, Louisiana State University School of Medicine, New Orleans; Senior Visiting Pathologist, Charity Hospital of Louisiana at New Orleans, etc. Pp. 763; 120 illustrations. New York: The Macmillan Company, 1939. Price, $4.50.

THE title "Medical Microbiology" is very appropriate, as the text includes fungi, mold-like higher bacteria, protozoa, rickettsiæ, spirochetes and viruses in addition to the true bacteria. Although distinctly medical in emphasis, the book is concerned primarily with fundamentals so may well be used by students interested in the general aspects of microbiology.

The book is extensively indexed and each chapter prefaced with a topical outline. Although there is no bibliography at the end of each chapter, one section of the appendix has been devoted to general, well-selected references. Another section of the appendix is devoted to review questions for each chapter.

Part I (236 pages) is devoted to fundamentals of microbiology. Many drawings, diagrams and photographs are employed which are very instructive. The historical treatise of the various phases of microbiology are very well done. Part II (59 pages) is devoted to the laboratory study of microorganisms. This, together with appendices A, B and C, constitutes a short but good practical summary of laboratory procedures. Part III (116 pages) is devoted to the subject of infection and resistance. This is short and concise with stress placed on fundamentals. Part IV (227 pages) is devoted to the microbiology of important infectious diseases. Here the discussion is grouped according to the regions of the body, such as infections

of the skin, mouth and throat, respiratory tract, eye and ear, genito-urinary tract and the intestinal tract. There are also chapters on wound infections; diphtheria; pneumonia; typhoid and paratyphoid fevers, dysentery, cholera; tuberculosis and leprosy; infections acquired from animals; important virus diseases; principal fungous infections and protozoan infections.

The discourse is very clear and practical. Fundamentals are stressed throughout. It is ineed a textbook and not a reference work. The book is to be recommended. H. M.

THE ENDOCRINE GLANDS. By MAX A. GOLDZIEHER, M.D., Endocrinologist, Gouverneur Hospital and Brooklyn Women's Hospital, New York, etc. Pp. 916; 271 illustrations. New York: D. Appleton-Century Company, Inc., 1939. Price, $10.00.

THIS book covers systematically the diseases of the endocrine glands and their treatment, with preliminary discussions of anatomy and physiology. References are given at the end of subdivisions of each chapter; those to foreign literature appear to predominate. It would seem that it might have been better to choose more wisely those references which are of special merit than to cover quantitatively such an immense range of work, much of which seems of little value, especially when the author states that he intends "to discuss only what we know as established facts and not what we think may be so even if it be a logical postulate to be verified by future observations."

The author is not a dispassionate critic, but sometimes accuses those whose views are not in accord with his own as governed by prejudice, or a "nihilistic viewpoint," and "shocking" dogmatism. The book is colored by the author's personal points of view, with many of which the present Reviewer disagrees. Examples of these are his emphatic statements that enlargement of the adrenal medulla with increased secretion is capable of causing, presumably frequently, chronic hypertension; his view that thyroid crisis is due to a sudden breakdown of adrenal cortical function; that there is antagonism between the thyroid and the posterior lobe of the pituitary; his inclusion among pituitary disorders, of the toxemia of pregnancy, angioneurotic edema, and what he speaks of as "pituitary retention syndrome"; his use, in addition to subcutaneous injection, of pituitary extract and adrenal cortical extract by oral administration, which he admits is "frowned upon by the spokesmen of 'organized medicine.'"

Case histories and many illustrations are of interest. I. Z.

THE MASSACHUSETTS GENERAL HOSPITAL. Its Development, 1900–1935. By FREDERIC A. WASHBURN, M.D., Director Emeritus. Pp. 643; illustrated. Boston: Houghton Mifflin Company, 1939. Price, $4.00.

ONE of the oldest and most distinguished of this country's hospitals, the Massachusetts General Hospital, has been as efficient in keeping its own history as in conducting its other activities. Its early history (1811–1851) was recorded by Nathaniel Bowditch, Secretary and Trustee; the period from 1851 to 1872 by the Rev. G. E. Ellis, Trustee; and the ensuing period to 1900 by Mrs. Grace Myers, Librarian. Its history in the twentieth century, the subject of the present volume, is covered by one who was Director during most of this period of great expansion. The author can thus speak at first hand of the developments of the hospital itself, of the laboratories, of the Phillips House for private patients, the Baker Memorial for people of moderate means, the special departments, the outpatient departments, the medical social service and many other activities that

reveal the magnitude and complexity of a great modern hospital. Thus the story is of interest and value, not only to those who want all the facts about their cherished institution, but also to those concerned with the history of American hospitals at a period of their most rapid expansion. The more formal story is lightened by an entertaining chapter of Recollections of Medical House Pupils, gathered by J. H. Means. Here most any ex-intern can relive his hospital days and most any reader can get instructive sidelights on the medical advances and hospital life of the period. Chapters on Administration, Case Records, Finance, and similar topics add further to the value of this excellent work. E. K.

Opuscula Selecta Neerlandicorum de Arte Medica. Fasciculus Quintus-Decimus quem Curatores Miscellaneorum quæ Vocantur Nederlandsch Tijdschrift voor Geneeskunde Collegerunt et Ediderunt. Petri Camperi Itinera in Angliam, 1748–1785. Pp. 264; many text illustrations and 17 plates. Amstelodami: Sumptibus Societatis, 1939.

This fifteenth volume of a series which has been appearing irregularly since 1907 gives five of Camper's Travel Journals to Great Britain, in the original Dutch on the left-hand pages, and in English on the right-hand pages. It is embellished with a Preface and an Introduction by B. W. Th. Nuyens, 43 pages of biographic notes and 17 large plates. Other of Camper's writings have already appeared in Vols. 12 and 13 of this series. E. K.

Pathogenic Microörganisms. A Practical Manual for Students, Physicians and Health Officers. By William Hallock Park, M.D., Late Professor of Bacteriology and Hygiene, New York University College of Medicine, and Director Emeritus of the Bureau of Laboratories of the Department of Health, New York City, and Anna Wessels Williams, M.D., Former Assistant Director of the Bureau of Laboratories of the Department of Health, New York City. Pp. 1056; 247 illustrations and 13 plates (some in color). Eleventh edition. Philadelphia: Lea & Febiger, 1939. Price, $8.00.

This edition is still "Park and Williams" as the revision was completed shortly before Dr. Park's lamentable death. The clearness, conciseness and practicability, so characteristic of Dr. Park's style, is evident throughout. It is medical microbiology to date.

The portions of the book devoted to bacteriology and immunology are very good. Part I, the general principles and methods of bacteriology, includes a chapter of 35 pages on bacterial variation by Dr. Philip Hadley and also a chapter of 12 pages on bacterial metabolism by Dr. Kenneth C. Blanchard. These two subjects are of vital interest to everybody concerned with bacteriology and immunology, no matter what phase of the subject might be their interest. Chapters written by authorities on these subjects are an asset to any text. Part II, the techniques and methods of bacteriology, contains 99 pages of very practical and important material. Part VIII is devoted to applied bacteriology, which includes the bacteriologic examination of water, air, soil, milk and shellfish and the practical use of disinfectants. These latter two sections, Parts II and VIII, make a very practical manual. Part III, the principles of infection and immunity, contains 9 chapters or 159 pages which in addition to being a good discussion is elucidated with charts, diagrams and outlines. Part IV comprised of 333 pages devoted to pathogenic microörganisms includes descriptions of the spirochetes and rickettsiæ in addition to the customary bacteria.

There are 6 chapters of 86 pages in Part V devoted to viruses and virus diseases which were written by Dr. Morris Schaeffer and are a credit to any textbook. The section on pathogenic yeasts, molds and actinomycetes, Part VI, was written by Dr. Fred D. Weidman. It is 54 pages in length and is the best treatise on this subject appearing in any American textbook. The section on pathogenic protozoa, Part VII, is 6 chapters, 63 pages, in length and is very good. References are included at the end of each chapter. The book is well indexed, very well edited, well printed and bound and is to be highly recommended. H. M.

MEDICAL CLIMATOLOGY. Climatic and Weather Influences in Health and Disease. By CLARENCE A. MILLS, PH.D., M.D., Professor of Experimental Medicine, University of Cincinnati. Pp. 296; 90 illustrations. Springfield, Ill.: Charles C Thomas, 1939. Price, $4.50.

"THE human habitat on earth is one of highly fluctuating characteristics. It at all times dominates man's energy level and general vitality, forever holding him down to a bare existence level in tropical lowlands, or driving him forward impetuously in stormy middle temperature regions. This drive fluctuates widely from day to day, season to season, and through the years and centuries. Especially does the medical profession need a thorough knowledge of these forces and their effects on human diseases and general health. Health itself assumes a much more dynamic force in some climates than in others, and with this comes a change in the general disease picture. Infectious diseases become less deadly, but there appear increasing signs of breakdown from overwork of the body machinery. The practice of medicine thus varies widely from climate to climate. In the response of people to this climatic drive, there will in every region be found people who fail to adapt, for whom a change of climate may offer the only hope for a normal existence. It becomes the physician's duty properly to advise these unfortunate individuals." These nearly verbatim quotations give the essence of the argument of this fascinating and highly important book. Every physician should read it: he will find here much that is helpful, instructive, interesting and provocative of speculation, thought and study.

R. K.

THE SURGERY OF PAIN. By RENÉ LERICHE, M.D. (LYON), LL.D. (GLASGOW), F.R.C.S. (ENG.) (Hon. Causa), etc., Professor of Clinical Surgery, University of Strasbourg. Translated and edited by ARCHIBALD YOUNG, B.SC., M.B., C.M., F.R.F.P.S.G., F.A.C.S. (HON.), M.D. (STRASBOURG) (Hon. Causa), etc.; Regius Professor of Surgery, University of Glasgow; Visiting Surgeon, Western Infirmary, Glasgow. Pp. 512. Baltimore: The Williams & Wilkins Company, 1939. Price, $6.50.

THE author of this work, a general surgeon, has devoted much of his life to the study of so-called intractable pain, investigated in both clinical and experimental fields. As a result, the author has contributed much to our knowledge of the derivation of pain and its treatment. His best known work is "The Diagnostic Value of the Abolition of Pain by Regional Novocainization" and the function of the sympathetic nervous system in the production of pain.

This comprehensive study of pain in relationship to surgical treatment discusses the general problem of pain and analyzes the various types in separate chapters. The pains considered are trigeminal and post-traumatic neuralgias, causalgia, pains caused by amputations, vasoconstriction, juvenile arteritis, angina pectoris, cutaneous cicatrices, visceral disorders and the

pains of inoperable or recurrent abdomino-pelvic malignant tumors. Each malady is reviewed thoroughly from the standpoint of cause, mechanism of pain production, rationale of treatment and the results of various forms of treatment. The book is interesting as it is written in lecture style, thus permitting the author to use open and frank discussion.

He gives both clinical and experimental data in support of his views and methods of treatment. Concerning these, several points bear comment. His interesting theory of the function of the sympathetic nervous system in the production of pain is not in agreement with that of leading physiologists. The evidence for his rejection of the accepted work of Head and Mackenzie on visceral sensory representation is not convincing. Complete section of the trigeminal nerve for trifacial neuralgia, as recommended by the author, is unwarranted when the pain does not involve the first division. On the other hand, alcoholic injections are admittedly temporary but quite satisfactory in the relief of trifacial neuralgia. In spite of these variances from accepted theories, the author's honest and critical analysis of each subject makes it a most valuable work for the clinician, investigator and surgeon.

R. G.

THE ART OF ANÆSTHESIA. By PALUEL J. FLAGG, M.D., Visiting Anæsthetist to Manhattan Eye and Ear Hospital; Consulting Anæsthetist to St. Vincent's Hospital, New York, and to Woman's, Sea View, Jamaica, Mt. Vernon, Flushing, Mary Immaculate and St. Mary's Hospitals, Far Rockaway, New York, etc. Pp. 491; 161 illustrations. Sixth edition revised. Philadelphia: J. B. Lippincott Company, 1939. Price, $6.00.

THE first 400 pages of this edition are the same as in the fifth, except for some changes in illustrations and a few added notes. This part of the book deals with nearly all phases of anesthesia from the author's viewpoint up to 1932. There are 7 added chapters in which an attempt has been made to cover some of the newer developments in bringing the book up-to-date. These include chapters on the carbon-dioxide absorption technique and the new drug, cyclopropane, which are brief and conservative. The remaining chapters discuss new techniques, dental anesthesia and analgesia, intubation of the trachea, causes of deaths from anesthesia, and pneumatology. The author, who is one of the pioneers of the present era of modern anesthesia, has stressed the need for improvement in the personnel of anesthesia staffs in most hospitals. He maintains that this branch of medicine should be able not only to care for surgical anesthesia, but also gas therapy, resuscitation, respiratory difficulties, plus teaching and research.

I. T.

NEW BOOKS.

Journal of Criminal Psychopathology, Vol. 1, No. 1, July, 1939. Editor: V. C. BRANHAM, M.D. Editorial Staff: H. R. WEISS, A.M., J. J. BROOKS, A.M., C. D. OWENS, A.B., J. RUBIN, M.D., J. SCHUYLER, A.M., W. G. ROSE, PH.B. Pp. 85; illustrated. New York: Woodbourne Institution for Defective Delinquents, New York State Department of Correction, 1939. Issued Quarterly, free of charge.

Primer of Allergy. A Guidebook for Those Who Must Find Their Way Through the Mazes of This Strange and Tantalizing State. By WARREN T. VAUGHAN, M.D., Richmond, Va. Pp. 140; illustrations by JOHN P. TILLERY. St. Louis: The C. V. Mosby Company, 1939. Price, $1.50.

Maternal Care and Some Complications. The Principles of Antepartum, Intrapartum, and Postpartum Care and of the Management of Some Serious Complications. Approved by The American Committee on Maternal Welfare, Inc. Edited by F. L. ADAIR, M.D. Prepared by W. C. DANFORTH, M.D., G. W. KOSMAK, M.D., R. D. MUSSEY, M.D., R. L. DE NORMANDIE, M.D., F. L. ADAIR, M.D., P. F. WILLIAMS, M.D., F. H. FALLS, M.D. Pp. 194. Chicago: The University of Chicago Press, 1939. Price, $1.50.

Proctology for the General Practitioner. By FREDERICK C. SMITH, M.D., M.Sc. (MED.), F.A.P.S., Proctologist to St. Luke's and Children's Hospital, Philadelphia; formerly Associate in Proctology, Graduate School of Medicine, University of Pennsylvania. Pp. 386; 141 illustrations and 3 color plates. Philadelphia: F. A. Davis Company, 1939. Price, $4.50.

A Handbook of Elementary Psychobiology and Psychiatry. By EDWARD G. BILLINGS, B.S., M.D., M.D. Cum Laude (IND.), Assistant Professor of Psychiatry, University of Colorado School of Medicine; Director, The Psychiatric Liaison Department of the Colorado General and Psychopathic Hospitals, etc. Pp. 271. New York: The Macmillan Company, 1939. Price, $2.00.

Opuscula Selecta Neerlandicorum de Arte Medica. Fasciculus Quintus-Decimus quem Curatores Miscellaneorum quæ Vocantur Nederlandsch Tijdschrift voor Geneeskunde Collegerunt et Ediderunt. Petri Camperi Itinera in Angliam, 1748–1785. Pp. 264; many text illustrations and 17 plates. Amstelodami: Sumptibus Societatis, 1939. (Review p. 719.)

The Papworth Village Settlement. Report of the Committee of Management and Medical Director for 1938. Presented at the Twenty-second Annual General Meeting of the Settlement, June 30, 1939. Pp. 65; illustrated. Cambridge: Papworth Hall, 1939.

Papworth Research Bulletin for 1938, Vol. 2, No. 1. The Sims-Woodhead Memorial Laboratory. Illustrated. Cambridge: Pendragon Press, 1939.

An Introduction to Medical Mycology. By GEORGE M. LEWIS, M.D., Associate, and Assistant Attending Dermatologist, New York Post-Graduate Medical School and Hospital, Columbia University; Instructor in Medicine (Dermatology), Cornell University, etc., and MARY E. HOPPER, M.S., Assistant in Mycology, Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University. Pp. 315; 71 full-page plates. Chicago: The Year Book Publishers, Inc., 1939. Price, $5.50.

Recent Advances in Medical Science. A Study of their Social and Economic Implications. By SIR EDWARD MELLANBY, K.C.B., M.D., F.R.C.P., F.R.S., K.H.P., Secretary to the Medical Research Council. (The Rede Lecture Delivered before the University of Cambridge on April 28, 1939). Pp. 62. Cambridge: At the University Press; New York: The Macmillan Company, 1939. Price, 75c.

A Text-book of Occupational Diseases of the Skin. By LOUIS SCHWARTZ, M.D., Medical Director, United States Public Health Service, in charge of Dermatoses Investigations, Washington, D. C.; Lecturer, Department of Dermatology and Syphilology, New York University, etc., and LOUIS TULIPAN, M.D., Clinical Professor of Dermatology and Syphilology, New York University College of Medicine; Consulting Dermatologist, Manhattan General Hospital, etc. Pp. 799; 116 illustrations. Philadelphia: Lea & Febiger, 1939. Price, $10.00.

A Topographic Atlas for X-ray Therapy. By IRA I. KAPLAN, B.S., M.D., Director, Radiation Therapy Department, Bellevue Hospital; Director, Division of Cancer, Department of Hospitals, City of New York, etc., and SIDNEY RUBENFELD, B.S., M.D., Associate Visiting Radiation Therapist, Bellevue Hospital; Instructor in Surgery, New York University Medical College, etc. Pp. 120; 55 full-page plates. Chicago: The Year Book Publishers, Inc., 1939. Price, $4.00.

NEW EDITIONS.

A Synopsis of Regional Anatomy. By T. B. JOHNSTON, M.D., Professor of Anatomy, University of London, Guy's Hospital Medical School. Pp. 462; 17 illustrations. Fourth Edition. Philadelphia: Lea & Febiger, 1939. Price, $4.50.

Principles of Chemistry. An Introductory Textbook of Inorganic, Organic, and Physiological Chemistry for Nurses and Students of Home Economics and Applied Chemistry. With Laboratory Experiments. By JOSEPH H. ROE, PH.D., Professor of Biochemistry, School of Medicine, George Washington University; Formerly Instructor in Chemistry, Central School of Nursing, Washington, D. C. Pp. 503; 53 illustrations and 4 plates. Fifth Edition. St. Louis: The C. V. Mosby Company, 1939. Price, $3.00.

There are relatively few changes in this edition. In bringing it up to date the most marked changes were made in the chapters on Structure of Matter, Vitamins and Internal Secretions. In the latter two chapters some of the recent developments in respect to structural chemistry have been included. The discussion of fundamental organic chemistry has also been enlarged and throughout the book there is a more liberal use of figures and and diagrams. Part II on laboratory experiments has remained practically unchanged except for the inclusion of a few questions on the various experiments. The structural formulas have been omitted from the appendix. J. J.

Microbiology and Pathology. By CHARLES F. CARTER, B.S., M.D., Director, Carter's Clinical Laboratory, Dallas, Texas; Consulting Pathologist, St. Louis Southwestern Railway Hospital, Texarkana, Arkansas, and Mother Frances Hospital, Tyler, Texas, etc. Pp. 755; 165 illustrations and 25 color plates. Second Edition. St. Louis: The C. V. Mosby Company, 1939. Price, $3.25.

Pathogenic Microörganisms. A Practical Manual for Students, Physicians and Health Officers. By WILLIAM HALLOCK PARK, M.D., Late Professor of Bacteriology and Hygiene, New York University College of Medicine, and Director Emeritus of the Bureau of Laboratories of the Department of Health, New York City, and ANNA WESSELS WILLIAMS, M.D., Former Assistant Director of the Bureau of Laboratories of the Department of Health, New York City. Pp. 1056; 247 illustrations and 13 plates (some in color). Eleventh Edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, $8.00. (Review, p. 719.)

Asthma. By FRANK COKE, F.R.C.S., with the Collaboration of HARRY COKE, M.R.C.S., L.R.C.P., Honorary Physician, Charterhouse Rheumatism Clinic. Pp. 266; 19 illustrations. Second Edition, fully revised and illustrated. Baltimore: The Williams & Wilkins Company, 1939 (A William Wood Book). Price, $4.00.

Experimental Pharmacology and Materia Medica. By DENNIS E. JACKSON, PH.D., M.D., F.I.C.A., Professor of Pharmacology, Materia Medica, and Therapeutics in the University of Cincinnati College of Medicine, etc. Pp. 906; 892 illustrations, including 55 color plates. Second Edition. St. Louis: The C. V. Mosby Company, 1939. Price, $10.00.

PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS.

UNDER THE CHARGE OF
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ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY
AND
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HERSEY PROFESSOR OF THE THEORY AND PRACTICE OF PHYSIC AT HARVARD UNIVERSITY, BOSTON, MASS.

THE MECHANISM OF INSULIN CONVULSIONS.*

STUDIES on the dehepatized animal by Mann[30] and by Mann and Magath[31a] in 1921 proved that a certain amount of sugar in the blood is essential for life and that hypoglycemia is accompanied by a characteristic group of symptoms in which convulsions usually occur. They also showed that the injection of *d*-glucose restores the animal in a condition of hypoglycemia to normal and that if glucose is administered to a dehepatized animal in amounts sufficient to maintain the concentration of sugar in the blood at the normal level, the characteristic symptoms of hypoglycemia do not occur. Banting and co-workers[2] reported in 1922 that in rabbits convulsions occurred when the level of the blood sugar fell to 45 mg. per 100 cc. of blood. Later authors, however, demonstrated by further work that the decrease of blood sugar to a specific level is not the sole cause of the convulsions. Thus, for example, Macleod[29] found in 1924 that convulsions may occur with a blood sugar of 67 mg. per 100 cc. of blood. At the same time he demonstrated that the blood sugar may be as low as 37 mg. per 100 cc. of blood without the appearance of convulsions. The conclusion was therefore reached that there exists no definite relationship between the occurrence of hypoglycemic convulsions and the actual level of the blood sugar. Fletcher and Campbell,[12] von Noorden and Isaac,[35] and Redisch[41] reported the occurrence of convulsions despite a considerably elevated blood sugar. Bornstein and Holm[4] confirmed this observation both in humans and in rabbits. Clough, Allen and Root[6] pointed out that in animal investigations convulsions may accompany a lowering of the blood sugar to only 66 mg. per 100 cc. of blood, whereas there may be no convulsions with a blood sugar tension of 30 mg. per 100 cc.

* Abridgment of section of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D. in Experimental Surgery.

of blood. Pénau and Simonnet[38] and Putter[40] likewise confirmed the observation of lack of association between convulsions and the level of the blood sugar.

Delezenne, Hallion and Ledebt,[9] Laqueur, Grevenstuk and de Jongh,[28] and Langecker and Stross,[27] investigating this problem, concerned themselves with the purity of the insulin preparations which were employed and learned that similar results were obtained with chemically pure extracts. Pollak[39] in 1924 expressed the opinion that the diminished tension of the blood *d*-glucose is not the direct and sole cause of the convulsions and that the immediate agent is either some substance which is mixed with the insulin or a toxic substance which is formed after the insulin has been injected into the animal body.

Many authors have attempted to find the cause in the nervous system. Thus, Noble and Macleod[34] formulated the hypothesis that after the injection of insulin some metabolic product is formed which exerts toxic effects on certain centers in the pons and medulla oblongata. Likewise Dickson and co-workers[11] wrote of the presence of similar products and considered the convulsive phenomena to be the result of irritation in the forebrain and midbrain. Houssay and co-workers[24] expressed the opinion that irritation of the labyrinth and vestibule calls forth the convulsions.

Kokubun[26] in 1927 formulated the hypothesis that the convulsions of so-called insulin hypoglycemia are dependent on the formation of degradation products of urea. The formation of these degradation products is in turn dependent on an acute disturbance of liver function which is reflected in an elevation of the ammonium nitrogen of the blood. Nagasawa,[33] working with rabbits, was, in fact, able to demonstrate an elevation of the ammonium nitrogen during insulin hypoglycemia but stated that it is impossible to explain the convulsions by this elevation alone.

There is still some question as to the anatomic origin of the convulsions of insulin hypoglycemia. Olmsted and Logan[36] in 1923 stated that decerebrate cats with the pituitary body left intact maintain a high blood sugar level which is not materially reduced by insulin, whereas typical insulin convulsions can be induced in decerebrate cats whose pituitary body has been removed. They further found that the blood sugar percentage in decapitate cats may be lowered by insulin and maintained below the convulsive level of normal cats without the development of convulsions. The conclusion was reached that the locus of action of insulin is on the bulbar centers, particularly the respiratory center. Kleitman and Magnus[25] concluded in 1924, on the basis of experiments on rabbits, that hypoglycemia leads in some way to an irritation of the medulla and to the convulsions. As far as I have been able to determine, there have appeared in the literature no reports of attempts to corroborate either of these pieces of work.

There is no unanimity of opinion regarding the existence of pathologic changes in the central nervous system resulting from hypoglycemia. But little information has been gleaned from experimental studies on animals. Rather characteristic cellular changes have been reported by Wohlwill,[47] Grayzel,[14] and Stief and Tokay.[43] However, the experience of others, who employed rabbits, coincides more with that of Baker and Lufkin[1] and indicates that there is no characteristic patho-

logic picture. Baker and Lufkin, Terbrüggen,[44] and Bowen and Beck[5] carried out careful histologic studies on cases of hypoglycemia and reported the finding of petechial hemorrhages throughout the central nervous system. Bodechtel[3] and Wohlwill[47] have reported extensive zones of degeneration in the cortex of the cerebral hemispheres. The microscopic picture of these zones was similar to those seen by Gildea and Cobb[13] as the results of anemia, by Spielmeyer[42] as the result of carbon monoxide poisoning and by Courville[7] in patients who had died after nitrous oxide anesthesia. The changes in the nerve cells were thus seen to be non-specific. Terplan[45] expressed a similar view after studying 3 cases in which the patients died as he result of insulin shock. In 1938 Moersch and Kernohan[32] reviewed the neurology and neuropathology of hypoglycemia and reported in detail 2 cases in which the patients died of chronic hyperinsulinism. They were able to describe lesions of the cortex which were "not simply the result of coma but of a definite, although not specific, degeneration which occurred antemortem."

It seems altogether reasonable to assume that the neurologic phenomena of the hypoglycemic state are the result of some physicochemical change in the nervous system that is bound up in some manner with the metabolism of carbohydrates. Present indications are that changes in the oxygen tension are at the bottom of these neurologic manifestations. Olmsted and Logan[36] were the first to suggest that anoxemia is an important factor in the genesis of hypoglycemic convulsions: "It may possibly be that through the lowering of the blood sugar certain oxidative processes become depressed to such a degree that the brain cells, which are known to be especially susceptible to lack of oxygen, are affected in much the same manner as in asphyxia." They noted (1) the similarities between the convulsions of insulin hypoglycemia and those of asphyxia and (2) the "dark and venous character" of the arterial blood when the sugar content was very low. In later experiments Olmsted and Taylor[37] found a slight fall in oxygen saturation of the arterial blood of dogs following insulin convulsions.

It remained for Holmes,[22] however, to point out that *d*-glucose is essential in the normal utilization of oxygen by brain tissue. He demonstrated that gray matter utilizes more oxygen than white matter or spinal nerves and emphasized that the increased oxygen uptake in the presence of *d*-glucose is dependent on the conversion of *d*-glucose to lactic acid. Moreover, Holmes and Holmes[23] found that the glycogen content of the rabbit brain is small and very variable. They therefore stated that "glycogen plays a comparatively unimportant (or obscure) part in the carbohydrate metabolism of the mammalian brain, and that the organ is dependent for lactic acid precursor directly upon glucose supplied to it by the blood." Himwich, Koskoff and Nahum[20] and Himwich and Nahum,[19a,b] however, have shown that both lactic acid and *d*-glucose are absorbed by the brain from the blood in normal, phloridzinized and depancreatized dogs. The brain does not convert or store these foodstuffs as glycogen. In depancreatized animals the respiratory quotient of brain remains unity—indicating the utilization of lactic acid—in the absence of insulin necessary for *d*-glucose oxidation. Holmes and Holmes[21,23] have shown that carbohydrate is oxidized by brain tissue but only after transformation to lactic acid.

Himwich[18] has pointed out the significance of this capability of brain tissue in affording it a factor of safety "in two available sources of energy—glucose or lactic acid." Holmes and Holmes have demonstrated that insulin diminishes the oxygen uptake of cerebral cortex and this has been confirmed by Wortis.[48] Since a low blood sugar is reflected in a low lactic acid level in the brain, Wortis expressed the opinion that the convulsions resulting from hypoglycemia act as a protecting mechanism by adding lactic acid—a food utilized by the brain—to the circulating blood medium.

The lactic acid content of gray matter apparently does not bear a direct relationship to the lactic acid content of the blood. Holmes and Holmes found a greatly decreased lactic acid content of the brain following an injection of insulin, while Dameshek, Myerson and Stephenson[8] and other investigators found no decrease in blood lactic acid during the hypoglycemic reaction. Furthermore, as early as 1923 Mann and Magath[31b] demonstrated that in totally hepatectomized dogs neither racemic nor *d*-lactic acid is effective in preventing the development of hypoglycemic symptoms, whether it is administered intravenously or through a jejunal stoma. They cautioned their readers, however, that these findings do not exclude the possibility that lactic acid may enter the cell in some other form and be utilized intracellularly.

In 1935 Dameshek, Myerson and Stephenson[8] attempted to study the mechanism of the neurologic symptoms of insulin hypoglycemia in man, chiefly by comparing the content of *d*-glucose and oxygen in the vessels supplying the brain and the arm before and after the intravenous administration of insulin. They made the following observations by comparing the results of analysis of samples of blood withdrawn as nearly simultaneously as possible from the brachial artery, the internal jugular vein and the basilic vein: (1) The uptake of *d*-glucose by the brain became materially reduced during the severe hypoglycemic reaction, although that of the arm usually became increased. (2) The uptake of oxygen by the brain varied indirectly with the severity of the insulin reaction, becoming much reduced during the most severe reactions. (3) The blood lactic acid became increased during the reaction, no differences between vessels being noted. They concluded that the marked diminution in the arteriovenous difference in content of oxygen during the severe insulin reaction may signify actual diminution in oxygen uptake by the brain; if this is true, the neurologic symptoms of the insulin reaction may be due to the effects of a lack of oxygen on the brain.

Employing the technique developed by J. F. Heymans and Kochmann[16] and DeSomer and J. F. Heymans[10] for perfusion of the isolated head of the dog, C. Heymans, Jourdan and Nowak[17] investigated the survival and revival of nerve centers following acute anemia. When the circulation of the perfused isolated head was interrupted, the palpebral, pupillary and motor reflexes disappeared after 3 to 4 minutes of acute anemia. The respiratory, cardioregulatory and vasomotor centers were at first excited but, after 4 to 5 minutes of arrest of circulation, they became paralyzed. The encephalobulbar centers, as well as the isolated head as a whole, were than apparently dead. The revival of the various nerve centers was investigated by reëstablishing the cir-

culation to the isolated head after periods of arrest of varying lengths. The observations were summarized as follows:

1. After an arrest of the circulation of 15 to 20 minutes, the palpebral and pupillary centers were definitely paralyzed, although the vasomotor and respiratory centers could be revived without difficulty.

2. When circulation to the isolated head was reëstablished after an arrest of 30 minutes' duration, the respiratory, cardioregulatory and vasomotor centers could be revived and could resume their activity. The respiratory center, formerly considered the most sensitive to anemia, could be revived and could resume its activity even after 60 minutes of apparent death.

In 1935 C. Heymans and Bouckaert[15] studied the revival of the various nerve centers in the intact dog by reviving dogs after varying periods of apparent death from asphyxia. Their experiments demonstrated that in the intact animal also the respiratory, cardioregulatory and vasomotor centers can be revived after arrest of circulation for 30 minutes. When the arrest of circulation was limited to 5 minutes or less, there was generally complete recovery of the functions of all the centers. However, when the circulation was interrupted for longer periods the revived dogs exhibited narcosis, coma, rigidity and hyperthermia, symptoms probably indicative of lesions in the cerebral cortex and hypothalamus. These regions are apparently much less resistant to anoxemia than the medullary centers. Comparable results have been reported by Winkelbauer.[46]

In conclusion, it may be stated that the signs and symptoms of insulin hypoglycemia are for the most part due to anoxia of the brain. Despite the fact that the center for hypoglycemic convulsions has been variously placed in the forebrain, midbrain, pons, medulla oblongata, labyrinth and vestibule, it seems much more logical to assume that the convulsions are due to abnormal impulses arising in the motor cortex. The convulsions are practically identical with those seen in idiopathic epilepsy and there is at present entire agreement that the convulsions of idiopathic epilepsy arise in the motor cortex. In hypoglycemia the explosions of abnormal nerve impulses are in all probability the expression of deficient utilization of oxygen by the cortical cells in the presence of a low blood sugar. Future advances in the medical therapy of hypoglycemia will no doubt come with the discovery of methods whereby the utilization of oxygen by the brain may be improved. At the present time, the only therapeutic means of obtaining this improvement is the injection of *d*-glucose.

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RADIOLOGY.

UNDER THE CHARGE OF
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ROENTGEN THERAPY OF INFLAMMATORY CONDITIONS.

In 1896, shortly after the discovery of Roentgen rays by Wilhelm Conrad Röntgen, a number of physicians became interested in this new light as a diagnostic agent. It soon became apparent that the radiation was capable of evoking a cutaneous reaction consisting of erythema, dermatitis and even ulceration. This biologic effect attracted the attention of several observers who suggested that the newly discovered rays might have therapeutic value. The action of Roentgen rays (or radium) on different kinds of tissue was investigated experimentally and from these investigations considerable knowledge was acquired concerning the cellular effects of exposure to the rays. The therapeutic value of the rays was tested first in connection with inflammation of the skin, tuberculous processes such as tuberculous adenitis and cancer of the

skin or of deeper structures. Encouraged by the favorable action of the rays in various types of pathologic conditions, their therapeutic effect on other conditions was gradually put to the test. It was found that an increasing number of inflammatory conditions often responded favorably to suitable irradiation.

Desjardins[2] credited Williams with including, as early as 1902, among the pathologic conditions found to respond favorably to Roentgen irradiation: herpes zoster, psoriasis, eczema, acne vulgaris and rosacea, prurigo, lichen planus, lupus vulgaris or erythematosus and tuberculous adenitis or peritonitis. Some of these conditions were treated with more or less success from 1 to 5 years earlier by different physicians, including Freund (1897), Albers-Schönberg (1897), Gautier (1897), Rudis-Jicinsky (1898), Pusey (1900), and several others. In the preface to Belot's important book, "Roentgen Therapy for Cutaneous Diseases" (1904), Brocq asserted that "roentgen therapy already dominates the treatment of skin diseases." Belot added as amenable to Roentgen therapy sycosis, blepharitis, rhinophyma and mycosis fungoides.

During the next 15 years, the treatment of many other forms of inflammation was investigated. Many radiologists, even today, are not yet aware of these early investigations and reports, some of which are notable examples of painstaking work and keen observation.

Between 1904 and 1910, the main factors which govern the action of Roentgen rays on cells were discovered. It was during this same period that, as far as the therapeutic effect of Roentgen rays on many varieties of inflammation is concerned, that small or moderate doses were found sufficient and usually were superior to large doses, such as those employed in the treatment of most malignant processes. This was especially true of acute inflammations, in which a single exposure to a small dose (10 to 50% of the erythema dose) often proved sufficient to arrest the pathologic process. In cases of chronic inflammation, larger but moderate doses (50 to 80% of the erythema dose) had to be given and the dosage repeated at intervals for some time to cure the lesions or to obtain maximal improvement.

To pathologists it has been long known that one of the prominent features of many forms of inflammation, and especially of acute inflammation, is leukocytic infiltration, the degree of which varies according to the species of bacteria responsible for the inflammation, and perhaps also according to the number of bacteria present. In other words, the degree of leukocytic infiltration varies with the virulence of the infecting microörganisms. In a large proportion of cases in which the inflammation is caused by pyogenic bacteria, notably by staphylococci (furuncle, carbuncle, abscess, acute adenitis), the favorable effect of proper irradiation can be observed within 2 to 24 hours and this effect continues to increase thereafter. If the lesion was irradiated during the early part of its course, the pain subsided and disappeared, although the pain might increase for an hour or 2 before it commenced to diminish. The swelling abated and the lesion gradually resolved. When the lesion was not irradiated until later in its course, the resolving effect of the rays was less striking; pain diminished just as in the case of lesions which were treated earlier, but the analgesic effect took place more slowly. When the lesion was irradiated after suppuration had started, the suppurative process was hastened and it was necessary to provide

drainage sooner than would be the case with similar lesions which were not exposed to Roentgen rays.

These changes described were observed in about 75% of the lesions treated. When the inflammatory process was due to infection by streptococci, exposure to Roentgen rays was not followed by any modification which could be recognized as an effect of the rays.

Numerous experiments on animals have established the fact that lymphocytes in lymph nodes, spleen, circulating blood, intestinal follicles, thymus gland and other structures in which lymphoid cells are to be found are the most radiosensitive of all the different kinds of cells in the body. The neutrophils and the eosinophils are less sensitive than the lymphocytes, but only slightly so. Mucus-secreting epithelial cells (found chiefly in the salivary glands, stomach and intestine, and bronchi) are slightly less sensitive than the neutrophils and eosinophils, but they seldom play an essential or important part in inflammatory lesions.

When structures made up largely of lymphocytes are exposed to a small or moderate dose of Roentgen rays (or radium), a certain proportion of these cells subsequently undergoes degenerative changes and many are destroyed; the proportion of lymphocytes thus influenced depends on the dose of Roentgen rays. Warthin's experiments showed that this action of the rays began during irradiation and could be perceived microscopically within $\frac{1}{2}$ hour after exposure; in other words, as soon as sections of the irradiated lymphoid structures could be prepared and examined. A small proportion of lymphocytes remained unaffected and served as a nucleus for subsequent regeneration of these cells, unless excessive or repeated irradiation had destroyed them all. Beginning during irradiation and perceptible soon thereafter, the cycle of cellular changes, as they affected the lymphocytes, increased for 2 to 3 days; then the metabolic activity of the remaining cells continued at an abnormally low level, especially in relation to mitosis, for 1 to 3 or more weeks. After this, the remaining lymphocytes gradually recovered their ability to multiply and, after a time, partial or complete regeneration of these cells took place. When lymphoid structures were irradiated repeatedly, at relatively short intervals, an increasing proportion of cells were affected, fewer cells were able to survive, and their ability to regenerate and to replace the destroyed cells diminished more and more or the cells disappeared completely.

Degenerative changes induced by irradiation in the neutrophils and eosinophils in the circulating blood did not become perceptible until 12 to 24 hours after exposure. A smaller proportion of cells was affected by a like dose, and the resulting cellular changes were similar to those observed in the lymphocytes, although regeneration took place at about the same time and rate as that of the lymphocytes.

When the affected cells disintegrated, a subsidiary step was that adjacent reticular cells in the lymphoid structures or in other tissues in the irradiated area assumed the rôle of phagocytes and ingested the destroyed leukocytes. These reticular macrophages played an important part in disposing of bacteria and other noxious materials.

In lymphoid structures, the lymphocytes destroyed by the rays were replaced by connective tissue, but the proliferation of these cells was slow and did not become apparent until much later. In the meantime, the rapid regeneration of lymphocytes repopulated the lymphoid fol-

licles and tended to mask the increase in connective tissue. It was only after repeated irradiation had brought about marked or permanent disappearance of the lymphocytes that the increase in connective tissue became evident. Lymphocytes, neutrophils and eosinophils, destroyed while circulating in the blood, are not replaced by connective tissue; their contents (antibodies, ferments and so forth) are liberated in the blood stream and exert their effects in the same or in some other region.

Destruction of leukocytes is a prominent, if not the outstanding, effect of exposure to the rays. When, in acute inflammation, some of the infiltrating lymphocytes, neutrophils and eosinophils are destroyed by the rays, the contents of these destroyed cells, including the antibodies and other protective substances which have already formed, inevitably must be liberated and scattered among the remaining intact cells. Under these circumstances, it seems probable that the protective substances may become even more effective than when they were held within the cells before irradiation. There is little ground for the assumption that irradiation increases the production of antibodies. On the contrary, experimental investigation has shown that irradiation tends to diminish the formation of antibodies.

A satisfactory explanation of the influence of Roentgen rays or radium on chronic inflammation must be based on the pathologic character of the lesions and on the known action of the rays (as disclosed by experiments) on the kinds of cells present in the lesions. Here proliferation of connective tissue is a more prominent feature than leukocytic infiltration. Chronic inflammatory lesions are characterized by varying degrees of central necrosis, caseous degeneration, calcification, or hyaline or amyloid changes; where any of these changes have occurred, the tissues are impervious to the action of the rays. The varying relative proportion of leukocytic infiltration and proliferation of connective tissue in any given lesion will therefore govern the response of the lesion to Roentgen therapy. For chronic inflammatory lesions, larger quantitative doses of rays are necessary and treatment must be repeated at intervals for some time if satisfactory results are to be obtained.

For acute inflammation, especially that due to infection by staphylococci or due to trauma, a single, small dose (from 10 to 50% of the erythema dose) is usually efficient and yields the best results. Occasionally, when a single exposure has not had the desired effect, a second exposure several days after the first may be indicated. The more acute the inflammation, the smaller the dose usually required.

It is important that the field of irradiation should not be confined too closely to the visible limits of the inflamed tissue, but should include a wide zone of apparently normal tissues. This is especially true when the inflammation is due to infection by virulent bacteria, such as streptococci or *Clostridium welchii;* in such instances, the advantage of having the rays act on leukocytes in the blood circulating through the inflamed region and all around it is of paramount importance. In treating these inflammatory lesions caused by highly virulent bacteria, good results have been obtained by using small doses and repeating them daily or twice daily over a period of several days. Roentgen rays generated at moderate voltage, such as from 100 to 150 kv. and filtered through 4 or 6 mm. of aluminum or through copper of equivalent filtration value,

are more effective than rays generated at 200 kv. or more. For chronic inflammation, generally, treatment must not be discontinued too soon. Even after the lesions and symptoms have disappeared, or have ceased to be active, it is wise to give the patient 1 or 2 additional treatments. The more chronic the lesion, the more essential is this precaution.

Hodges and Snead[4] stressed (1) the value of the roentgenogram for disclosing unsuspected infections of sinuses and (2) the definite therapeutic value of irradiation for some types of sinus infection. Reviewing the literature on the experimental work done on this subject they arrived at the following summary of the effect of irradiation on infected membranes of the sinuses: "The effect of the *x*-ray treatment appears to be due primarily to an early destruction of the lymphocytes in the infected membranes. From 48 to 72 hours after treatment . . . . there appears to be an increase in the number of macrophages. . . . . These macrophages are seen to be laden with cellular débris and dead pigments. It is possible they also engulf bacteria. The membrane becomes gradually reduced in thickness but retains numerous plasma cells, polymorphs, and some histiocytes. After a week or more some fibrosis appears. There is no evidence of injury to the cilia, epithelium, or cellular elements other than the lymphocytes as the result of *x*-ray dosage."

Hodges and Snead obtained their best results in cases classified clinically as subacute or subchronic, in which symptoms were present for a period varying from several months to several years. Many of these patients have a cough and give a history of recurring colds and on roentgenologic examination of the thorax, exaggeration of the bronchovascular markings of the lower lobes is found. Roentgenologic examination of the sinuses discloses cloudy ethmoids with marked thickening of the membrane in the antra. They obtained good results with irradiation in the majority of cases in which symptoms were present for several years, usually with hyperplastic sinusitis and roentgenographic findings of marked cloudiness of the ethmoids and much thickening of the membranes in the antra. In these two groups of cases when roentgenographic examination disclosed an increase in the bronchovascular markings, small doses of irradiation were applied over the lungs with definite benefit.

In the group of cases in which early or reasonably early polypoid changes were found, especially in the nose, with a history of infection for many years, marked relief followed irradiation in the majority of cases. A number had return of the sense of smell and 2 had much improvement in vision following treatment. Others who were unable to breathe through the nose were relieved in this respect. Some who required repeated operations for removal of polypoid material had no recurrence of polypoid hyperplasia. Usually, the longer the duration of the infection or the more chronic and widespread the polyp formation, the poorer were the results from irradiation.

In the experience of Hodges and Snead, coöperation of the rhinologist and radiologist in the diagnosis, and follow-up of the results of treatment were essential for best results.

In the cases characterized by infection, 130 kv. with 6 mm. of aluminum filtration, about 300 r measured in air, was given in 3 or 4 treatments over a period of from 1 to 3 weeks. In those cases characterized

by polypoid hyperplasia, 200 kv. with 0.5 to 2 mm. of copper filtration, 600 r measured in air, was used.

It is an accepted fact that bronchiectasis frequently is associated with infection of the accessory sinuses of the nose. Hodges and Snead mentioned the benefit obtained from irradiation of the lung when accentuation of the bronchovascular markings was evident. Berck and Harris[1] reported the successful use of irradiation in the treatment of chronic suppurative bronchiectasis. In an analysis of the factors concerned in the results obtained, after a review of the experimental work on animals and a correlation of the experimental results with those obtained by irradiation among human subjects, these authors concluded that the effect was owing to possible enhancement of immunizing processes both through the action of the rays in stimulating antibody action and the physicochemical alterations of the local tissue reactions rather than to diminution or abolition of secretion. They thought it most logical to assume that the results obtained were due to the action of the Roentgen rays on chronic inflammatory processes.

Roentgen therapy was instituted in a series of cases of chronic suppurative bronchiectasis. All patients subjected to treatment had been observed previously over a period of several months at least, and were known to have a chronic lesion with sustained high level of expectoration without marked spontaneous remissions. All these patients were investigated thoroughly by means of bronchography and bronchoscopy and the diagnosis of chronic suppurative bronchiectasis was clearly established. The majority of the patients were variously and unsuccessfully treated by bronchoscopic drainage and lavage, pneumothorax, phrenic nerve interruption, and climatotherapy. Roentgen therapy was given as a last resort. The alternative for these patients was radical operative intervention, such as lobectomy or pneumonectomy.

To control observations on the effect of the treatment, no other form of therapy was used coincidentally. The patients were ambulatory, for the most part, during treatment. Roentgen therapy was given over a period of approximately 3 months, cross-firing all the diseased and secreting lobes (as revealed by bronchography and bronchoscopy) through anterior, lateral and posterior fields, utilizing 3 portals for one lobe or 5 for the hemithorax, as necessary. The physical factors were: 180 to 200 kv.; 0.5 mm. copper plus 1 mm. aluminum filtration; the focal skin distance was 50 cm. Each treatment consisted of 75 r, measured in air, to two or three fields. The patients usually were treated 2 to 3 times a week; the average total dose used was approximately 1500 r through each port of entry. At least 4 months was allowed to elapse after irradiation to secure the full measure of improvement. If the lungs were involved bilaterally, the authors found it of advantage to treat both sides simultaneously.

Patients who previous to treatment had experienced hemoptysis and episodes of pneumonitis were free of such attacks and episodes subsequent to treatment. A large proportion of all patients was relieved of cough and expectoration. Clubbing of the digits subsided surprisingly in a number of cases. Improvement was sustained during all the follow-up examinations, in some cases over a period of 6 years. During this period, infections in the upper part of the respiratory tree were experienced repeatedly by their patients, characterized by slight

increase in expectoration but this was without odor, and there was no recurrence of harassing cough and no profuse, foul expectoration. In several of the most severe cases, great improvement was experienced and this has been sustained without recurrence for more than 6 years. The symptomatic improvement in the majority of cases has been striking.

During the course of treatment, the patient's symptoms may be exaggerated, which may lead to discouragement on the part of the patient and also on the part of the therapist. This is a definite part of the effect of radiation encountered in the treatment of this disease.

Powell[5] reported the use of Roentgen therapy in 105 cases of lobar pneumonia and in 30 cases of bronchopneumonia. As soon as the diagnosis was made on the basis of the history, the physical examination, the condition of the blood and the roentgenologic examination, treatment was commenced. A definite leukopenia such as is found associated with some postinfluenzal pneumonias was the only contraindication to Roentgen treatment in his experience. Treatment was given anteriorly or posteriorly over an area a little larger than that represented by the involved portion of the lung. Using 135 kv. with 3 mm. of aluminum filtration and a target skin distance of 40 cm., a dose of 250 to 350 r was given. If the temperature had not returned to normal or to below normal within 36 hours after the first Roentgen treatment, a second treatment of 200 r was given over the opposite cutaneous area. When Roentgen treatment was given before consolidation was complete, consolidation might spread, but the patient would show the usual clinical improvement, and the temperature, pulse, respiration and number of leukocytes would return to normal. A few cases with mixed infection required a third or fourth treatment, using, of course, successively smaller doses so as to avoid a cutaneous reaction. Bronchopneumonia seemed more variable in its response to radiation therapy, but Powell was of the opinion that Roentgen therapy materially reduced the mortality rate of this condition.

Patients were treated in all stages of the disease, from the first day to, in 1 case, the eleventh day. Most of the patients were relieved of distress and experienced general symptomatic improvement within a few hours, and in more than one-third of these cases the temperature decreased to normal within 36 hours after treatment.

Dowdy, Heatly and Pierce[3] used radiotherapy as an adjunct in the treatment of acute otitis media in a series of 30 cases, with encouraging results. The character of the discharge either remained thin or became thin after irradiation. This resulted in adequate drainage of the middle ear cavity. With the reduction of congestion, the Eustachian tube tended to be more completely patent, thus adding to the patient's comfort. Occasionally, drainage from the middle ear was established by this channel

Using 200 kv., 25 ma. and 50 cm. target distance with 0.485 copper plus 1 mm. filtration, 100 r units were administered over an area sufficiently large to include the ear, mastoid region and posterior nasopharynx. Most of the patients required only 1 treatment. If the condition responded slowly and if immediate operation was not indicated, a second treatment was given within 48 to 72 hours. Of the 30 patients treated, 25 had 1 treatment each and 5 had 2 treatments each.

The irradiation seemed to be of distinct value in relieving the acute symptoms and in shortening the course of the disease. The average duration for the acute, purulent, uncomplicated cases was shortened 6 days, while that of the complicated cases was shortened 16 days. The clinical improvement when the treatment was effective was much more striking than these figures would indicate. The necessity for operation apparently was reduced.

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